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VOLUME 42

1928

PUBLISHERS

AMERICAN MEDICAL ASSOCIATION

CHICAGO

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THYROID DISEASE

AN EXPERIMENTAL STUDY *

WARREN B. COOKSEY, M.D.
AND
M. S. ROSENBLATT, M.D.
DETROIT

The pathogenesis, classification and treatment of the diseases of the thyroid gland continue to be subjects of considerable controversy. Although the etiologic relationship of the thyroid gland to exophthalmic goiter was at one time considered definitely proved, a small group of dissenters have maintained that the thyroid gland cannot be considered more than a single link in the chain of a complicated disease.

Hoover,[1] for example, said:

> Men write very freely about the excessive flow of internal secretions from a hyperplastic thyroid into the circulation, but this is certainly not true of myxedema and it has never been proved to be true in Grave's disease. In fact, no one has thus far offered anything but inferential or fancied evidence for hyperthyroidism, and that has been so feeble that it will not stand critical inspection.

Israel Bram [2] went even further, and said:

> The question involved is not that of a "lump on the neck." We must firmly understand that a subject of Grave's disease is no more a victim of goiter than is a sufferer with typhoid fever one of splenomegaly.

Hyman and Kessel [3] said:

> In our opinion, exophthalmic goitre is a complicated disease, based on a disturbance in the involuntary nervous system, activated by some sympathomimetic factors, of which infection and psychic trauma are examples, and superactivated, if you will, so that there is produced a metabolic upset whose origin is obscure—which may be thyrogenic, but which probably is not.

Solis-Cohen [4] said:

> The neurogenic theory of the origin of exophthalmic goiter is the older one, displaced largely through Kocher's work. Some observers, however, of whom

* From the Buhl Laboratory and the Surgical Service of the Harper Hospital.

1. Hoover, C. F.: Does Hyperplasia Offer any Evidence for the Thyrogenesis of Graves' Disease? Am. J. M. Sc. **173**:11 (Jan.) 1927.

2. Bram, Israel: The Prevention of Exophthalmic Goiter, Endocrinology **7**:415 (May) 1923.

3. Hyman, H. T., and Kessel, L.: Exophthalmic Goiter and Involuntary Nervous System, J. A. M. A. **85**:1017 (Oct. 3) 1925.

4. Solis, Cohen, S.: In discussion of Hyman and Kessel (footnote 3).

I am one, have held to it throughout. We look on the goiter and the symptoms of dysthyroidism as incidents and epiphenomena. They may or may not be present.

The point of view adhered to by many of the clinicians who do not favor the thyrogenesis of exophthalmic goiter is that one is dealing with a group of patients who by hereditary and acquired predisposition become susceptible to an exciting cause capable of setting up an improper balance of the autonomic and endocrine systems.

On the other hand, the advocates of the thyrogenesis of exophthalmic goiter are numerous. Most surgeons feel that the removal of the thyroid gland is indicated in exophthalmic goiter and in most cases are able to hold out great hopes for a complete cure. Richter,[5] for example, reported 100 cases in which the patients were operated on for "thyrotoxicosis" and claims that 99 of the patients were relieved of hyperthyroidism after operation. He says: "Aside from all question of the exciting cause, the immediate source of the clinical syndrome called exophthalmic goiter lies entirely within the thyroid gland. Its removal is incompatible with the continued existence of the disease in its various forms."

Crile [6] said:

> In hyperthyroidism, the thyroid gland is the druggist, an extraordinary druggist, a tireless druggist, who day and night is manufacturing and turning into the circulation the exciting hormone." He further says[7]: "Taking into account the slight primary risk and the promising immediate and remote results of operation, we now consider in the case of hyperthyroidism as in that of appendicitis that the indication for operation is diagnosis."

In these introductory remarks, we have used the term exophthalmic goiter because we feel that the syndrome of exophthalmic goiter gives a clearer picture to most clinicians than any other term we might have selected. However, obviously the question of hyperthyroidism is not solely concerned with the syndrome of exophthalmic goiter. Hypersecretion of the thyroid gland is just as much a question in those cases of so-called "thyrotoxicosis" in which the syndrome of exophthalmic goiter is not present or is incompletely present. It is our opinion that it is impossible to distinguish any reliable pathologic differences in the various types of so-called hyperthyroidism, no matter what the mode of onset or the presenting clinical picture.

---

5. Richter, H. M.: Thyroidectomy: Its Relation to the Cure of Thyrotoxicosis, J. A. M. A. **88**:888 (March 19) 1927.

6. Crile, G. W.: Certain Problems in the Treatment of Diseases of the Thyroid Gland, J. A. M. A. **83**:813 (Sept. 13) 1924.

7. Crile, G. W.: Surgical Treatment of Hyperthyroidism, South. M. J. **16**: 459 (June) 1923.

In view of the conflicting opinions presented, it was our desire at the onset of this investigation to attempt to obtain more conclusive proof or disproof regarding the question of altered or excessive thyroid secretion in exophthalmic goiter and allied diseases. In the past, numerous attempts have been made to settle this question, and in reviewing the literature we found rather conflicting data. Hara [8] reported that the blood in cases of exophthalmic goiter exerted an effect like thyroxin in increasing metabolism. On the other hand, Wilson and Kendall [9] found that the thyroid gland in cases of toxic goiter contained but one-fifteenth to one-twentieth as much thyroxin as found in patients with normal glands. Hunt [10] reported that the acetonitril test for thyroid secretion was positive in the blood from patients suffering with exophthalmic goiter, whereas in blood from normal patients the test was not positive. From the experimental data derived from the various commercial sources using desiccated thyroid preparations or thyroid extracts, it has become clear that animal thyroid preparations vary in potency, and that the variation is proportional to the iodine content of the glands. But the thyroid gland in exophthalmic goiter has a noticeably low iodine content, Jolin,[11] Wells,[8] Weir.[12] Oswald [13] found that the physiologic activity of thyroglobulin obtained from goiters was the same as that obtained from patients with normal glands, except that it was weaker in direct proportion to the amount of iodine it contained, being free from effect in the total absence of iodine.

Feeding experiments in which goitrous glands from human beings were used seem surprisingly rare. Lenhart [14] fed thyroid glands from people to tadpoles, including glands affected by simple and exophthalmic goiters, and he stated that they all acted alike qualitatively. Abderhalden and Schiffman [15] also conducted feeding experiments, and they, too, con-

8. Hara, in Wells, H. G.: Chemical Pathology, Philadelphia, W. B. Saunders Company, 1925, p. 696.

9. Wilson and Kendall: The Relationship of the Pathological Histology and the Iodin Compounds of the Human Thyroid, Am. J. M. Sc. **151**:79, 1916.

10. Hunt, Reid: Acetonitril Test for Thyroid and of some Alterations of Metabolism, Am. J. Physiol. **63**:257, 1923.

11. Jolin, in Wells, H. G.: Chemical Pathology, Philadelphia, W. B. Saunders Company, 1920, p. 604.

12. Weir, J. F.: Thyroxin and Tryptophane Content of the Diseased Thyroid Gland, Am. J. M. Sc. **169**:860, 1925.

13. Oswald: Ueber die Wirkung der Schilddrüse auf den Blütkreislauf, Arch. f. d. ges. Physiol. **164**:506, 1916.

14. Lenhart, C. H.: The Influence on Tadpoles of Feeding Desiccated Thyroid Gland, J. Exper. Med. **22**:739, 1915.

15. Abderhalden and Schiffman: Studien ueber die von einzelnen Organen hervorgebrachten substanzen mit spezifescher Wirkung, Arch. f. d. ges. Physiol. **195**:167, 1922.

cluded that the physiologic activity of preparations from goitrous glands was the same as that from normal glands, and that it varied directly with the iodine content. These experiments have not seemed entirely conclusive to us, however, and in view of the fact that one of us (W. B. C.),[16] had previously conducted thyroid feeding experiments for another purpose, we decided to repeat this work on a more comprehensive scale.

The basis of the experimentation is derived from the pioneer work of Gudernatsch,[17] in which he demonstrated that tadpole larvae when fed thyroid gland preparations would undergo complete metamorphosis in a much shorter time than normally. Subsequent work has not only confirmed this fact, but demonstrated that the change in form by the larvae is a direct expression of the stimulation of metabolism (Lenhart[14]).

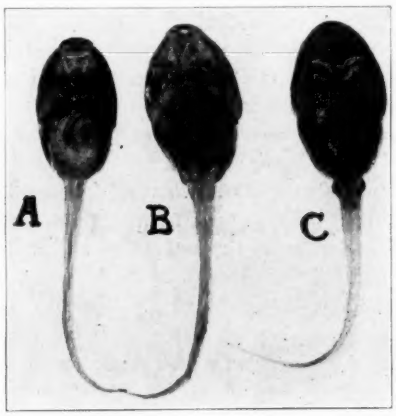

Fig. 1.—Normal metamorphosis of amphibian larva, Rana Pipiens. *A* shows tadpole aged *2* weeks; *B*, *3* weeks; *C*, 5 weeks. Note the appearance of posterior limb buds in *C* and the disappearance of simple coiled intestine.

Swingle,[18] by his admirable work in this field, pointed out the influence of organic iodine and allied substances on tadpole metamorphosis and warned against the tadpole test in determining the thyroid potency of commercial preparations. By using proper controls and by a comparison of iodine contents, we feel that Swingle's suggestions are not applicable in the following experiment.

16. Cooksey, W. B.: The Influence of Thyroid Feeding on the Brain of Rana Pipiens, Endocrinology **6**:393 (May) 1922.

17. Gudenatsch, J. F.: Feeding Experiments on Tadpoles, Am. J. Anat. **15**: 431, 1914.

18. Swingle, W. W.: Is the Tadpole Test for Thyroid Valid? Endocrinology **8**:832 (Nov.) 1924.

EXPERIMENTAL WORK

In conducting the experiment, we used the thyroid glands from thirty persons operated on for goiter over a period of two months. These glands were taken from the operating room to the laboratory as quickly after their removal as possible. In the laboratory, the gland was stripped of fatty and fibrous tissue, and after suitable sections for microscopic study had been removed, the gland was cut into small pieces, care being used not to lose any of the juice of the tissue. The thyroid which had been cut was spread on large watch glasses, carefully weighed and then placed in a vacuum desiccator over calcium chloride. The glands were desiccated at room temperature and were usually dry in twenty-four hours, although for uniformity they were left in the desiccator four days. After desiccation, the glands were placed in a large mortar and ground into a fine powder. The fresh and dry weight was

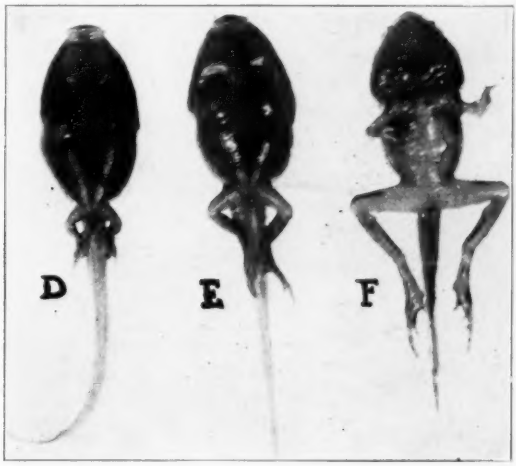

Fig. 2.—Normal metamorphosis continued. *D* shows tadpole aged 6 weeks; *E*, 7 weeks; *F*, 9 weeks. Note the limb buds, shortening of the tail, and adult appearance of the snout. The latter occurs as the gills disappear.

recorded in each case. By Kendall's method,[19] the iodine content was determined, each determination being checked at least twice.

The larvae used were hatched from fresh eggs of *Rana pipiens* obtained through the courtesy of the University of Michigan biologic department. Tadpoles of similar age and size were carefully selected, and each lot was given a control period of from five to seven days. The control food consisted of one part egg yolk, two parts powdered clover leaves and eight parts of flour mixed together in a paste and spread out in a thin layer to dry. This food, consisting of thin flakes, was easily ground to small pieces suitable for feeding even extremely small larvae. The food which contained thyroid was prepared in a similar way, each ingredient being carefully weighed and each preparation containing

19. Kendall, E. C.: Determination of Iodine in Connection with Studies in Thyroid Activity, J. Biol. Chem. **43**:149, 1920; **19**:251, 1914.

sufficient thyroid powder to be exactly equivalent to 4 Gm. of fresh gland. The food was fed to the larvae once daily, each bowl being the same size and containing the same number of tadpoles, while a similar amount of food was fed each lot. The complete feeding experiment was repeated three times, tadpoles of various ages being used for a comparative study.

The results of our experiments are shown in the table. However, there are several important details that warrant further elaboration.

By reference to the table, it is obvious that, except for slight variation, glands removed from patients who bore marked clinical signs of

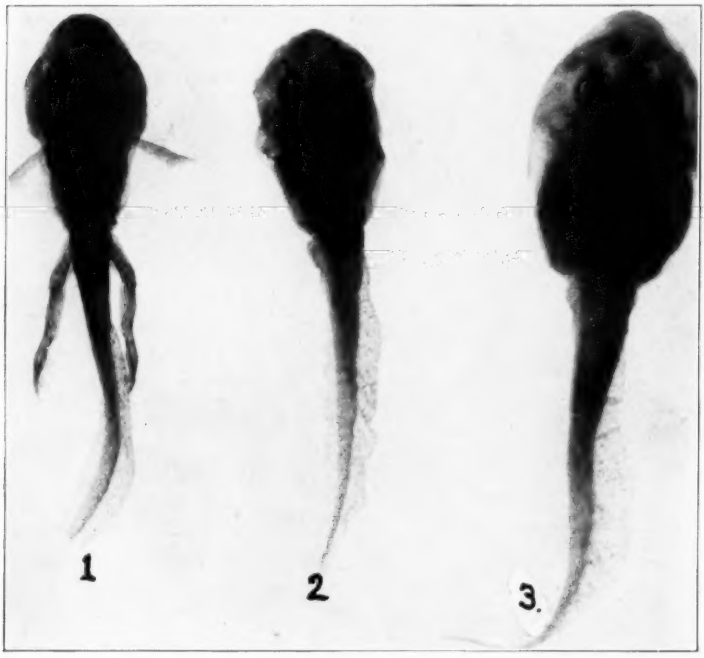

Fig. 3.—Acceleration of the metamorphosis by thyroid feeding for eight days in larvae aged 4½ weeks. *1* is a representative specimen from lot fed exophthalmic goiter gland, gland from case 4 being used; *2*, specimen from lot fed normal human gland; *3*, specimen from lot fed normal food. Note how nearly complete is the metamorphosis of larva *1*, which was fed the goiter gland.

thyroid toxicity, namely, tachycardia, nervousness, loss of weight, etc., were able to produce a parallel situation in the experimental larvae; that is, extremely toxic goiter glands produced a more marked acceleration of larval metamorphosis than was produced by the less toxic or normal gland. This will be more clearly seen by reference to figures 4 and 5, which represent cases 4 and 7 with their controls.

Representative Specimens of the Experiment

Case	Weight of Gland	Iodine Content	Diagnosis	Basal Metabolic Rate	Degree of Involution	Duration of Symptoms	Postoperative Reaction	Clinical Activity of Case	Experimental Activity of Gland			Comment
									Lot 1	Lot 2	Lot 3	
2	19.6	2.24	Normal human gland	....	.....	.....	.....	....	I	I	I	Normal gland obtained at autopsy
3	70.9	4.24	Old adenoma—toxic	+84	Advanced	Enlarged 15 years, symptoms 1 year	Moderate	IV	III	III	IV	Developed exophthalmos 3 weeks before operation; gland was degenerated in center
4	55.4	1.98	Late primary hyperplastic	+56	Moderate	2½ years	Death in storm	IV	IV	III+	IV	Had severe hemorrhage 1 hour postoperative; died in storm 15 hours postoperative
5	82.1	2.96	Early primary hyperplastic	+76 +46	Moderate	Few months	Very slight	I	I	II	I	Weakness the only symptom
6	81.5	3.56	Old adenoma—toxic	+62 +31	None	Enlarged 12 years, symptoms 1 year	Severe	III	II	II	III	Central portion of gland degenerated; microscopic hemorrhages
7	35.9	3.92	Primary hyperplastic	+19	Advanced	8 months	Very severe	IV	IV	IV	IV	Typical rapid primary hyperplasia with lymphoid areas
8	32.3	1.56	Early primary hyperplastic	+82 +63	Very slight	3 to 4 months	Severe	III	II	II	III	Single lobectomy
9	25.1	4.04	Primary hyperplastic	+80 1st oper. +26 2d operation	Advanced	1 year	Very slight	III	IV	III	II	Single lobectomy 3 months previous with much relief
10	21.8	1.58	Primary hyperplastic	+71 1st oper. +51 2d operation	Moderate	.....	Slight	II	I	I	I	Ligation and lobectomy 3 months previous with much relief
11	131.0	1.06	Colloid adenoma	....	Complete	Enlarged 20 years, symptoms 1 year	Very slight	I-II	I	I	I	Gland cystic with much central degeneration
12	38.0	5.34	Late primary hyperplastic	+55	Moderate	3 years	Very severe	IV	IV	IV	III	Single lobectomy
13	20.2	3.04	Early primary hyperplastic	+28	Slight	1 year	Very slight	I	0-I	I	0-I	Had much rest, roentgen-ray treatment and compound solution of iodine
14	31.1	2.54	Simple colloid (?)	+20 + 2	Complete	4 to 5	Slight	I	I	I	I	Firm glistening gland; diagnosis not clear

* Note how closely the clinical activity of the glands used parallels the experimental activity, in the larvae fed on thyroid. All weights are in grams of fresh gland and iodine contents are in milligrams of iodine per gram of dry gland. Lot 1 represents larvae 10 days old at the beginning of the feeding; lot 2, larvae 14 days old, and lot 3, larvae 26 days old.

REPORT OF CASES

CASE 4.—A negro, aged 27, had had symptoms of exophthalmic goiter for two and one-half years. He was extremely nervous, had marked tachycardia, had lost 50 pounds (22.7 Kg.) in weight and had exophthalmos, tremor and lid lag. He had a rather severe hemorrhage two hours after operation, which was con-

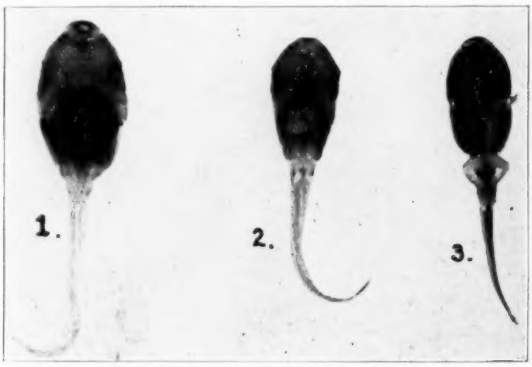

Fig. 4.—Representative specimens from lot 3 of experimental larvae. Tadpoles were 26 days old and were fed experimental food for seven days. *1* shows specimen fed normal food; *2*, specimen fed normal human thyroid; *3*, specimen fed goiter gland from case 4. Note the anterior and posterior limb buds in *3* and the close proximity to adult form.

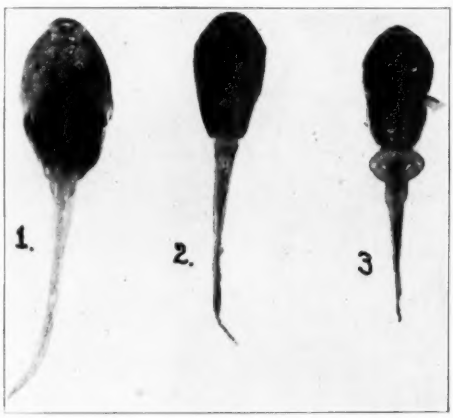

Fig. 5.—Representative specimens from lot 3 of experimental larvae. *1* shows specimen fed normal food; *2*, specimen fed normal human thyroid; *3*, specimen fed goiter gland from case 7. Note the almost complete adult form of tadpole *3*.

trolled, but he died fifteen hours later in a typical thyroid storm. A diagnosis of primary hyperplastic goiter, with the syndrome of exophthalmic goiter was made. The tadpoles from the lots fed glands from patients nos. 3 and 12 showed a similar acceleration of development.

Figures 4 and 5 show that practically a complete change to adult form occurred in those larvae to which goiter glands were fed. Both anterior and posterior limb buds are present, the tail length is decreased, and an adult form is obvious. Since in all the feeding experiments, exactly the same amount of fresh gland was used in each lot, one must conclude that the thyroid gland in these cases actually contains more active principle than is normal.

Case 11 is an example in which the thyroid from a case of nontoxic goiter was used (figs. 6 and 7).

Case 11.—A woman, aged 31, had had a large thyroid for twenty years. Four years ago, during her last pregnancy, the thyroid increased in size, and she was slightly nervous and tired easily.

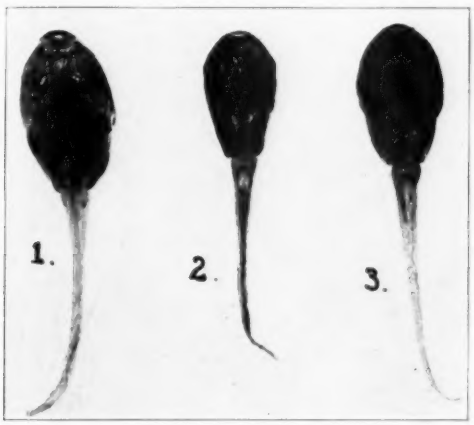

Fig. 6.—Representative specimens from lot 3 of experimental larvae. *1* shows specimen fed normal food; *2*, specimen fed normal human thyroid; *3*, specimen fed goiter gland from case 11. Note that tadpole *3* is little changed from the specimen fed normal food; the tail is not shortened, the snout is little changed, and posterior limb buds are just appearing.

She had never had tremor or exophthalmos, or lost weight and her blood pressure was normal. Both lobes of the gland weighing 134 Gm. were removed, and she had a slight postoperative reaction. A diagnosis of colloid adenoma was made (fig. 6 and case 11 in table; see also cases 13 and 14 in table).

Apparently these glands were not able to accelerate tadpole metamorphosis greatly, for the larvae were not even as fully developed as were the ones which had been fed with normal human glands.

Figure 8 and cases 3 and 6 in the table are examples of toxicity arising on the background of old adenomas.

Case 6.—A woman, aged 57, first noticed enlargement of the thyroid gland twelve years before admission to the hospital. For one year she had had symptoms

which consisted of nervousness, palpitation and tremor. She had lost 12 pounds (5.4 Kg.) in weight, and her basal metabolic rate was + 62 per cent and + 32 per cent before operation. She was extremely toxic. A large, friable gland was removed, which weighed 81.5 Gm., and in the center of which was a large area of degeneration. Microscopic examination showed numerous hemorrhages. She had a severe postoperative reaction.

As seen by the figure, this gland was able to accelerate larval metamorphosis almost as much as the gland in case 4, in which there was a primary hyperplastic goiter with the syndrome of exophthalmic goiter.

The iodine content of normal thyroid gland preparations has been shown repeatedly to be closely correlated with the activity of the preparation. But in these experiments, we have found that the iodine content is

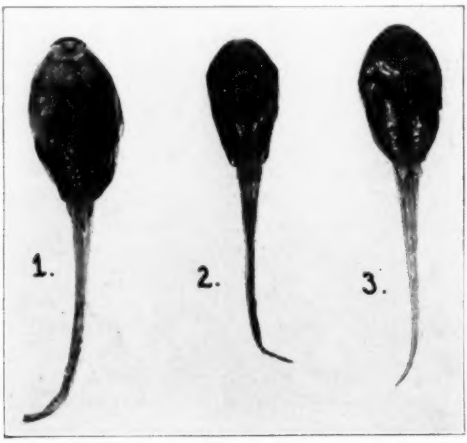

Fig. 7.—Representative specimens from lot 3 of experimental larvae. *1* shows specimen fed normal food; *2*, specimen fed normal human thyroid; *3*, specimen fed goiter gland from case 13. The patient in case 13 had a mild primary hyperplastic goiter and had had much rest, roentgen-ray treatment, and compound solution of iodine. Note that *3* shows little change over *1*, which was not fed thyroid.

by no means the only factor involved in abnormal gland preparations. It must be considered that practically all of the patients from whom these glands were removed had been given compound solution of iodine. For that reason, the iodine content of the glands is abnormally high. One might, therefore, expect certain abnormal factors to be present in the feeding results due to the organic iodine itself. However, there is not one exception to the rule that the glands removed from clinically toxic cases are able to produce marked acceleration of metamorphosis regardless of the iodine content of the gland used. Cases 4, 7 and 12 illustrate this fact extremely well, for regardless of the low iodine con-

tent in case 4, experimentally it proved just as active as case 7 or 12, in which the iodine content was much higher. Also, in cases 9 and 13, the goiters are of the primary hyperplastic type; because of previous operation or roentgen-ray treatment plus much rest and iodine, a low clinical toxicity is present. Although these glands had a high iodine content, they were not able to exert a pronounced effect on larval metamorphosis.

It will be noted that those glands with a high iodine content were more toxic for lots 1 and 2 of the tadpoles than they were when fed to lot 3. This was evident by the extreme emaciation and early deaths of the larvae of lots 1 and 2 when active glands with high iodine contents were fed to them. This is due to the fact that lots 1 and 2 represented

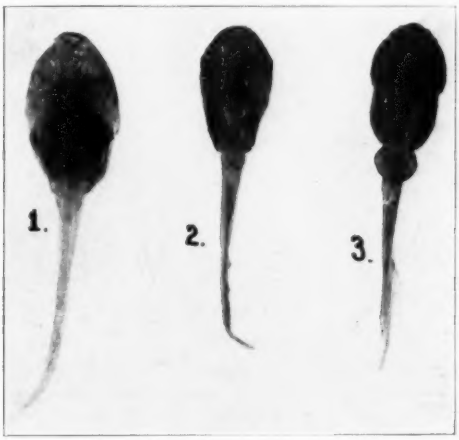

Fig. 8.—Representative specimens from lot 3 of experimental larvae. *1* shows specimen fed normal food; *2*, specimen fed normal human thyroid; *3*, specimen fed goiter gland from case 6.

larvae only 10 and 14 days old, respectively, while the tadpoles used in lot 3 were all 26 days old. As also reported by other workers, the younger larvae are much more easily killed by thyroid and organic iodine than the older larvae; hence much more reliable data may be obtained when the older tadpoles are used, since in them the larvae are able to proceed to more complete changes before toxic effects are manifest.

In order to check further the question of iodine content, food was prepared by the addition of iodcasein (Mulford) to the food otherwise prepared as before. Sufficient iodcasein was added to each preparation, so that the total organic iodine was 5.34 mg. per gram of thyroid. This gave a value, such that each preparation contained the amount of iodine

present in gland no. 12 in which the iodine content was highest. This food was now fed as before to a separate lot of tadpoles. We were unable to detect the slightest difference in the tadpoles fed this food from those in lot 3 who were started at about the same age, but who were fed the thyroid preparation without the addition of extra iodine.

In conclusion, we feel that these experiments have shown by biologic test that the thyroid gland in exophthalmic goiter contains quantitatively more active principle than is present in either the normal human thyroid or the thyroid of patients with less toxic goiter. They have further shown that the amounts of active principle demonstrable in the gland by these tests on amphibian larvae is directly proportional to the clinical activity of the patients from whom the glands were derived. Certain glands removed at operation apparently contained large amounts of this

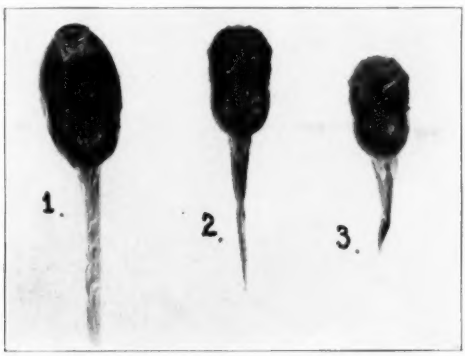

Fig. 9.—Representative specimens from lot 2 of experimental larvae. The tadpoles were 14 days old and were fed the experimental food for eight days. *1* shows specimen fed normal food; *2*, specimen fed normal human thyroid; *3*, specimen fed goiter gland from case 7. Note the emaciation, shortened tail and change of intestinal form in the larvae fed on thyroid. At this age many of the larvae die from the toxic effects before metamorphosis has proceeded far.

active principle, while others contained smaller amounts, and some apparently contained less than the normal amount. There has not been a direct correlation between this test and the iodine content of the glands, thus showing that in these goitrous glands iodine content is not a reliable measure of activity. While the majority of these patients had been given a compound solution of iodine, it had been given in variable amounts and for various lengths of time, and a few had received practically no iodine. This is also shown by the degree of involution of the glands. If the contention is correct that a compound solution of iodine causes a binding of thyroid secretion in the gland, we should expect those cases which had been completely iodized and which had shown complete

glandular involution to be most potent experimentally. This was not the case, and, as some have contended, it is probably due to the fact that the large amount of colloid material evident by microscopic examination in these involuted glands is not the active thyroid secretion, but stored colloid. Perhaps the storage of this inactive colloid temporarily inhibits secretion of the true thyroid principle. Certainly there was no correlation, as far as we could see, between the degree of involution change and the experimental activity.

SUMMARY

1. The question of excessive thyroid secretion in exophthalmic goiter and allied diseases is discussed, and the various claims for and against hyperthyroidism are presented.

2. Feeding experiments were conducted in which various types of goitrous glands from human beings were fed to tadpole larvae. There is evidence from these experiments that thyroid glands from clinically active cases of goiter actually contain more active thyroid principle per unit weight than the normal thyroid. Other goitrous glands contained less active principle by this biologic test, and the amounts were directly proportional to the clinical activity of the patient. Old nontoxic adenomas contained less active principle per unit weight than normal, while one gland which had had much roentgen-ray treatment and rest also contained less active principle per unit of weight.

3. By these experiments, hypersecretion of the thyroid gland in exophthalmic goiter and other clinical thyrotoxic cases seems definitely proved.

CARDIAZOL

SOME EXPERIMENTAL EFFECTS OF THIS DRUG ON THE CARDIORESPIRATORY MECHANISM *

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AND
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Much has been written of late, especially in the continental medical journals, as to the value of cardiazol (penta-methyl-tetrazol). It has been recommended especially in cases of acute cardiovascular collapse and respiratory failure. Glowing reports are appearing of its use in varied conditions, such as pneumonia, surgical shock, intrapartum asphyxia, auricular fibrillation, angina pectoris, diabetic coma, scopolamine depression and other conditions. The bulk of these reports, however, are of poorly controlled clinical observations made on a small number of cases, usually from three to six, when other stimulants had previously been given. It is our purpose in this paper to give a short summary of the pharmacology of cardiazol and to report some experimental work concerning the points for which it is most recommended.

Camphor has long been used as a cardiac stimulant, especially in acute conditions and in moribund states. Lewin,[1] in 1890, and Schwalb,[2] in 1912, found it to be a depressant. Joachinoglu,[3] in 1916, was unable to substantiate previous favorable reports; they also believed that it was a cardiac depressant. Heathcote[4] found that the administration of camphor intravenously produced a sharp fall in the blood pressure, and concluded that "there is no convincing pharmacologic evidence that camphor possesses any value whatever as a cardiac or circulatory stimulant." Sollmann[5] felt that its effects were inconstant and unreliable, and that no conclusions could be drawn from experimental work on animals. Cushney[6] said: "There is no reason to believe that camphor, in even the largest therapeutic doses, has any effect after absorption

* From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine of the Harvard Medical School.

1. Lewin, A.: Arch. f. exper. Path. u. Pharmakol. **27**:226, 1890.
2. Schwalb, H.: Arch. f. exper. Path. u. Pharmakol. **70**:70, 1912.
3. Joachinoglu, G.: Arch. f. exper. Path. u. Pharmakol. **80**:259, 1916.
4. Heathcote, R. A.: J. Pharm. & Exper. Therap. **21**:177 (April) 1923.
5. Sollmann, T.: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1922, p. 493.
6. Cushney, A. R.: Pharmacology and Therapy, Philadelphia, Lea & Febiger, 1924, p. 72.

except a slight dilatation of the skin vessels." Marvin and Soifer [7] arrived at similar conclusions from clinical observations.

An occasional striking result, however, is apparently obtained from the use of camphor, and investigation has been continued in an attempt to find some active principle in the drug. Most organic groupings having an effect on the heart have been found to be limited to the organic nitrogen compounds. The alephatic amines have little if any effect, and most of the aromatic amines are too toxic for prolonged use.[8] The imadazol ring seems ineffective, but little has been done with the tetrazol group.

Schmiederberg and Meyer [9] felt that since camphor is insoluble and is suspended in oil, the irregular therapeutic responses were due to the variability of absorption, hence an inconstant dosage. Various forms and isomers of camphor have been investigated. Gottlieb and Schuleman [10] synthetically produced a camphor substitute, 3 methyl — 5 isopropyl — 2-3 cyclohexanon (Hexeton-Bayer), soluble in 20 per cent aqueous solution of sodium salicylate. Schmidt and Hildebrandt [11] found that camphor effects were not limited to the members of the terpene group soluble with difficulty, but could be produced by several compounds of the nitrogen-polymethylene series. One of this series Schmidt [12] developed by the action of two molecules of hydrazoic acid on cyclohexanon, giving the compound sold under the name Cardiazol. Schmidt has claimed it to be pentamethylentetrazol.*

Schmidt and Hildebrandt [12] found cardiazol stable to heat, readily soluble, quickly absorbed and not cumulative. The extraordinary absorptive quality rendered it practically as effective when given subcutaneously as when given intravenously, as regards dosage and reatcion time. They reported a stimulating effect on the heart of the frog, rat and rabbit, both in normal and in depressed states (chloroform) when isolated and intact hearts were used. Respiration depressed by morphine was improved, and they considered that the cortex of the brain was "powerfully stimulated by cardiazol." They, therefore, concluded that cardiazol was distinctly an improvement on camphor. Experimentally, they found a

* In the preliminary report of the Council on Pharmacy and Chemistry (J. A. M. A. **90**:2019 [June 23] 1928) it was recommended that the name Metrazol be used instead of "Cardiazol."

7. Marvin, H. M., and Soifer, J. D.: Value of Camphor-in-Oil as a Cardiac Stimulant, J. A. M. A. **83**:94 (July) 1924.

8. Wolf and Sherman: Clin. Med. **33**:8 (Aug.) 1926.

9. Schmiederberg and Meyer: Ztschr. f. Phys. Chem. **3**:422, 1924.

10. Gottlieb, R., and Schuleman, W.: Deutsche med. Wchnschr. **49**:1536 (Dec.) 1923.

11. Hemmerling: Deutsche med. Wchnschr. **51**:1618, 1925.

12. Schmidt, K. F.: Hildebrandt, F., and Krehl, U.: Klin. Wchnschr. **4**:1678 (Aug. 27) 1925.

definite effect within from thirty to sixty seconds when given intravenously, and in from one to three minutes when given subcutaneously. Toxic effects were obtained in rats with a dose of 10 mg. per hundred grams of body weight and lethal effects with 15 mg. Rabbits showed toxic manifestations with from 10 to 15 mg. per kilogram of body weight and convulsions with doses of from 20 to 30 mg. when given intravenously, and from 30 to 40 mg. per kilogram when given subcutaneously. Eichler and Hildebrandt [13] found the blood pressure to be slightly depressed and the heart rate slightly decreased.

Stross [14] found that the heart of a normal frog was unaffected by cardiazol, and that large doses had a chronotropic and inotropic action, the heart finally stopping in diastole. He depressed the action of the heart by several methods, including that used by Schmidt and Hildebrandt (chloroform) and concluded that cardiazol was frequently of help, but not nearly as effective as either caffeine or epinephrine. After cardiazol had failed, cardiac arrest produced by potassium and ox gall was overcome by epinephrine, on the one hand, and by caffeine, on the other. He found, however, a marked increase in the blood pressure, which was not obtained in the decerebrate animal. Schoen [15] experimentally caused depression in rabbits until the vestibular reflex was lost, and found that cardiazol was beneficial; it was not beneficial, however, if the depression was carried much deeper.

In an attempt to clarify some of the rather conflicting reports, a series of experiments on cats has been carried out in this clinic to determine the toxic and lethal doses. Effects on the action of the heart, blood pressure and respiration were then observed in the anesthetized animal; finally, the same observations were made in various experimentally produced states of depression.

EXPERIMENTAL TECHNIC

Thirty-five adult cats were used, and several experiments were performed with many. They were placed on an animal board in the dorsal position, and carried under light ether anesthesia. The right fore leg and the left hind leg were shaved, and the customary lead II electrocardiograms were made. The left femoral artery and vein were exposed, and 0.1 Gm. of heparin [16] was dissolved in 2 cc. of physiologic sodium chloride solution and injected intravenously. A cannula was inserted in the left femoral artery and connected with a mercury manometer by means of a rubber tube containing 3 per cent acacia solution under slight pressure. Clamps between the cannula and the manometer were then

13. Eichler, O., and Hildebrandt, F.: Arch. f. exper. Path. u. Pharmakol. **116**:110, 1926.

14. Stross, William: Arch. f. exper. Path. u. Pharmakol. **114**:177, 1926.

15. Schoen, R.: Arch. F. exper. Path. u. Pharmakol. **113**:257, 1926.

16. Gordon, B.; Matton, M., and Levine, S. A.: J. Clin. Investigation **1**:497 (Aug.) 1925.

removed, and a graphic record of the arterial pressure was traced. A pneumograph was placed about the cat's chest and connected with a tambour, and a similar tracing of the respiration was recorded. Medication was given intravenously and subcutaneously. Ten per cent solution of cardiazol (Knoll[17]) in ampules was used throughout this study. A neutral 1 per cent solution of quinidine sulphate (U.S.P.) in doses of from 6 to 30 mg. per kilogram was employed to depress respiration and heart action and to lower the blood pressure in one series of experiments,[18] while 0.5 per cent solution of sulphuric acid was used for the same purpose in another.[18] Caffeine sodiobenzoate in physiologic sodium chloride solution was given in doses of 10 mg. per kilogram.

TOXIC, SUBLETHAL AND LETHAL EXPERIMENTS

Cardiazol was given to anesthetized animals in doses of from 1 to 15 mg. per kilogram. Such doses go well below and above those recommended for clinical use. In this group of eight animals, no favorable respiratory, cardiac, blood pressure or electrocardiographic changes were noted, but frequently, a decided depression of blood pressure and heart

Chart 1.—In this and the following charts the upper tracings show respiration and the lower show blood pressure. At the bottom, time is indicated in intervals of ten seconds. In the other figures, although time is not indicated, the same measurements obtain. Cardiazol, 1.5 mg. per kilogram was given intravenously at *A*, and 10 mg. per kilogram at *B*. Note that respiration is not affected except by a definite slowing with the second dose. The blood pressure fell slightly with the small dose and more markedly with the larger dose; the total fall was from 160 to 136 mm. of mercury. The pulse amplitude markedly deminished.

action occurred (chart 1). Total amounts as large as 480 mg. per kilogram were without a toxic effect when given in small divided doses (from 3 to 5 mg. per kilogram) at intervals of six minutes. This indicates that there is little if any accumulation, for much smaller amounts were lethal when given in single doses.

Toxic manifestations developed constantly within from forty-five to ninety seconds after intravenous administration, with doses of about 35 mg. per kilogram. Fine fibrillary twitchings appeared first about the

17. We are indebted to E. Bilhuber of New York for a liberal supply of this drug that was used in this investigation.

18. Bayliss, W. M.: Intravenous Injection in Wound Shock, Brit. M. J. **2**: 553, 1918.

lips, the eyes and in the legs. Various degrees of generalized muscular spasticity frequently occurred and occasionally a convulsion of varying severity and duration. There were peculiar changes in the respiration. At first, there was a deep inspiration accompanied by generalized muscular spasms, and the respiration was held in this position (chart 2). After from sixty to ninety seconds, shallow and rapid respiratory phases ensued, resulting in embarrassed aeration with cyanosis of the lips and tongue. This condition gradually passed off, usually restoring the respiration to a normal rate and amplitude in from twelve to eighteen miuutes. These experiments showed that the doses from 35 to 70 mg. per kilogram were toxic, but not lethal. The severity of the toxic symptoms varied with the amount injected.

Single doses of 80 mg. or more per kilogram were lethal in every case (seven experiments), whether given intravenously or subcutaneously. The animals showed the usual toxic symptoms about a minute after administration, then quieted down, only to resume terrific tonic convulsions about one and one-half hours later; these convulsions were

Chart 2.—This chart illustrates the toxic results from 35 mg. per kilogram of cardiazol given at *A*. Note first a cessation of respiration at *B*, animal held breath in deep inspiration and showed fibrillary twitchings. The respiration was regular. From *C* to *D*, there were convulsions. The animal recovered.

fatal. The blood pressure was decreased in varying amounts, and the only significant fact noted in the electrocardiographic tracings was a slight slowing of the heart rate (an average of from 165 to 150) and an occasional inversion of the T wave. Postmortem examination showed a rigid, outstretched animal, with much froth about the nostrils and mouth. The intestines were in a spastic state, and the heart was arrested in systole. Gross changes of the central nervous system were not noted.

EXPERIMENTAL COLLAPSE

A sharp fall in the blood pressure of from 60 to 70 mm. of mercury, produced by neutral quinidine sulphate in doses of from 6 to 9 mg. per kilogram, was not benefited by cardiazol. Doubling the foregoing doses of quinidine produced a decrease in the rate and amplitude of respiration in addition to the customary fall in blood pressure. The patient was not improved by the use of cardiazol (chart 3). Not only was there failure to support respiration and blood pressure, but frequently the depression

was made definitely worse by cardiazol. In fact, occasionally the depressed state from which recovery was to have been expected proved to be fatal after even a small dose of cardiazol. Such an experience was well illustrated in chart 4. Here a moderate depression of respiration and blood pressure was first obtained by the administration of 5 mg. per kilogram of quinidine, from which state a complete recovery ordinarily takes place in from twelve to fifteen minutes. In this instance, the customary recovery was taking place when cardiazol was given. The return of blood pressure was almost immediately arrested and followed by a cessation of respiration, slight convulsion, failure of heart action and death.

Doses of 30 mg. per kilogram of neutral quinidine sulphate produce a fall in blood pressure of 100 mm. or more of mercury and cause respiration to cease. It is in such a state of shock that a cardiovascular or

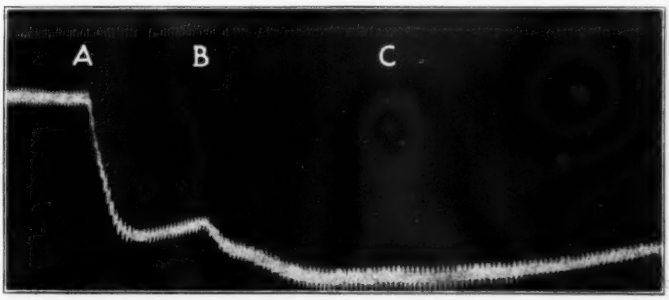

Chart 3.—At *A*, 7.5 mg. per kilogram of neutral quinidine sulphate was given intravenously. Note the marked customary fall in blood pressure (from 180 to 116 mm. of mercury) and slight depression of respiration. At *B*, the same dose of quinidine was repeated with further depression (blood pressure fell to 95 mm. of mercury). At *C*, 20 mg. per kilogram of cardiazol was given with no appreciable effect on blood pressure or respiration. The slight recovery of blood pressure is less than seen following quinidine without cardiazol.

respiratory stimulant would be of great value. Therefore, in a number of experiments, cardiazol was given while the heart was still beating. Small doses of from 1 to 20 mg. per kilogram did not have any effect and larger doses (from 20 to 40 mg.) seemed to kill the animal promptly. Although cardiazol did not have a stimulating effect in such marked states of collapse, caffeine alone or with artificial respiration, as observed by Gordon, Matton and Levine,[16] had a prompt and astounding restorative action. This was well illustrated in chart 5; 30 mg. of quinidine per kilogram was given (part 1, chart 5), producing a fall of 80 mm. in blood pressure and cessation of respiration. Although the blood pressure was greatly reduced, the action of the heart was good, as indicated by the

electrocardiographic record taken simultaneously and by the pulse excursions made on the kymograph. Ten milligrams per kilogram of cardiazol was then given, and a further fall in blood pressure followed with a marked diminution in the pulse. Ten milligrams of caffeine sodiobenzoate was then given, and the pulse rate showed definite improvement, but there was no evidence of return of the respiration; therefore, artificial respiration was instituted at about the rate and rhythm of the normal animal. Respiration quickly returned, the action of the heart improved, and the blood pressure began to rise. A few minutes later (part 2, chart 5), quinidine was given, this time rather slowly so that we might obtain a depressive effect on the respiration without killing the animal. Twenty milligrams per kilogram again caused a fall in the blood

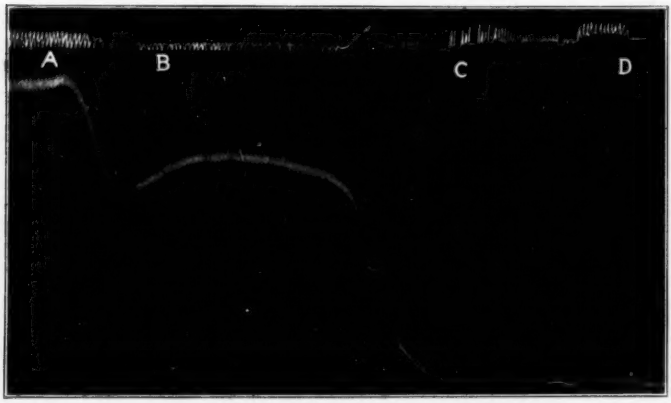

Chart 4.—At *A*, 5 mg. per kilogram of neutral quinidine sulphate was given intravenously. Note the fall in blood pressure (from 156 to 86 mm. mercury), with customary beginning recovery. At *B*, 7 mg. per kilogram of cardiazol was given. Note the marked fall of blood pressure with essential arrest of the heart and finally cessation of respiration and death despite artificial respiration between *C* and *D*. This shows that cardiazol aggravated the depressed state.

pressure, a decrease in the pulse amplitude and almost a cessation of the respiration. At this point, 10 mg. per kilogram of caffeine was given. A remarkable and prompt return of respiration, heart action and blood pressure followed. The animal recovered, and a better state was present than just before the second dose of quinidine was given; in fact, the cat seemed in almost as good condition as when the experiment was started; therefore the administration of quinidine was repeated (part 3, chart 5). This time the dose was only 10 mg. per kilogram, but it was followed by a fall in blood pressure of 15 mm. and a moderate decrease in rate and amplitude of respiration. At this point, 10 mg. per kilogram of

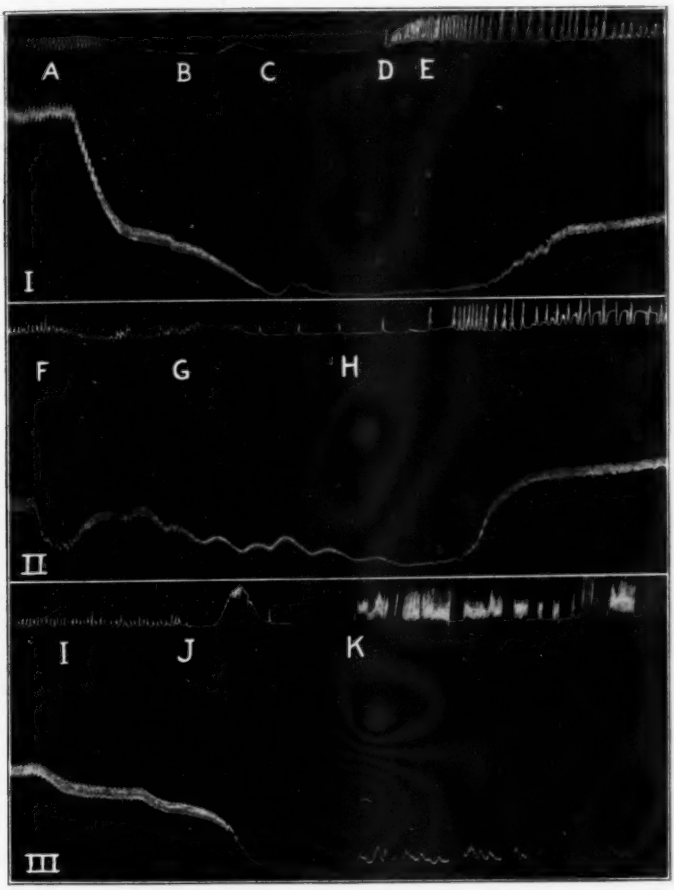

Chart 5.—Intervals of about ten minutes lapsed between upper tracing (I) and middle (II) tracing and between middle and lower tracing (III). At *A*, 30 mg. per kilogram of neutral quinidine sulphate was given. Note the marked fall in blood pressure (from 190 to 110 mm. of mercury) and cessation of respiration. At *B*, 10 mg. per kilogram of cardiazol was given, followed by a further fall in blood pressure (from 110 to 76) and a decrease in pulse amplitude. At *C*, 10 mg. per kilogram of caffeine sodio-benzoate was given. A slight increase in pulse amplitude resulted, but no effect on respiration. Between *D* and *E*, artificial respiration was followed with prompt improvement of circulation and respiration. Between *F* and *G*, 20 mg. per kilogram of quinidine was given slowly. Respiration almost ceased, pressure fell and pulse amplitude diminished. At *H*, 10 mg. of caffeine sodio-benzoate was given with prompt recovery. At *I*, 10 mg. per kilogram of quinidine sulphate was given with a slight depression and at *J*, 10 mg. per kilogram of cardiazol, which resulted in further depression. The animal died despite artificial respiration and cardiac massage (*K* to *L*). This experiment shows that cardiazol failed to improve the depressed state under circumstances in which caffeine restored the circulation, and finally, that cardiazol was fatal when the animal would have otherwise recovered.

cardiazol was followed by the same type of depression as that noted in part 1 of chart 5. Artificial respiration was tried, then both artificial respiration and cardiac massage was carried out for a prolonged time; however, the animal died in much the same manner as in the experiment illustrated in chart 4. Recovery was to have been expected if this final dose of cardiazol had not been given. The foregoing experiments show definitely not only that cardiazol failed to improve animals in artificially depressed states, but that it even aggravated the condition.

Further methods of inducing a state of shock or depression were employed in order to test the value of cardiazol. Experimental hemorrhage was produced by removing varying amounts of blood. From fifteen to fifty cubic centimeters of blood was withdrawn from a vein, causing varying falls in blood pressure (chart 6). Then cardiazol in several different sized doses was given, but improvement was not

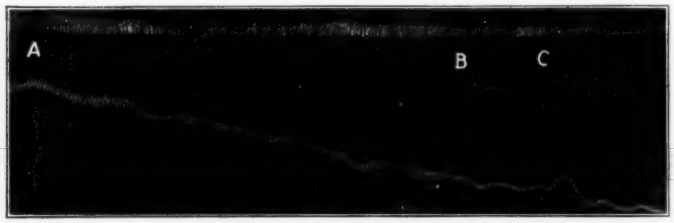

Chart 6.—From *A* to *B*, 25 cc. of blood was removed from the femoral vein. Blood pressure fell from 190 to 140 mm. At *C*, 25 mg. per kilogram of cardiazol was given which produced a slight further depression. The animal slowly recovered. This shows the failure to obtain improvement in the depression produced by hemorrhage.

obtained in four experiments. Likewise, shock was produced by the injection of from 2 to 10 cc. of 0.5 per cent solution of sulphuric acid intravenously.[17] In other experiments, acid was given after a brief period of starvation or in conjunction with a slight hemorrhage. Cardiazol did not prove to be of any value in counteracting the depression in any of these experiments.

CONCLUSION

In a series of experiments on cats it was found that cardiazol did not have any beneficial effect on the cardiorespiratory mechanism. This was true in the normal animal and in states of depression, produced by quinidine, hemorrhage and acid intoxication.

THE ELECTROCARDIOGRAM IN DIPHTHERIA *

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Circulatory failure has long been recognized as a frequent cause of death in cases of diphtheria. Investigators differ as to the exact mechanism of this process. Some believe that the fall of blood pressure and the circulatory collapse is a result of a myocardial weakness, while others insist that it is due to primary failure of the vasomotor apparatus, either central or peripheral.

Electrocardiographic studies [1] made during the acute stage of the infection show evidences of myocardial damage in a majority of cases Changes during the acute period are chiefly those of disturbances in auriculoventricular and intraventricular conduction. It is well known that in the late and convalescent periods, an acute collapse or sudden death may occur, usually after slight exertion. There are no reliable clinical criteria by which such a cardiac involvement may be detected during this stage. With a view of determining whether the string galvanometer may give this evidence, a study was made of a group of patients with diphtheria during the convalescent period. Readings were taken of fifteen patients with severe and moderately severe cases of diphtheria during the period of convalescence, usually in the third or fourth week of illness. In all cases, the local condition of the throat had entirely cleared up and the cultures for diphtheria bacilli were negative. The general symptoms of toxemia had disappeared and practically the only abnormality was a heart beat which readily increased in rate. In seven of the fifteen cases, significant abnormalities were seen in the electrocardiogram. The following is a report of these cases.

REPORT OF CASES

CASE 1.—J. D., a man, aged 35, admitted to the contagious hospital on Sept. 10, 1922, had been ill with a sore throat for three days before admission and had received 20,000 units of diphtheria antitoxin on the fifth day. After seven days in the hospital, he showed paralysis of the soft palate. Examination of the heart on September 15 did not reveal any abnormality. He was discharged on September 21

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1. Rohmer, P.: Electrocardiographische und anatomische Untersuchungen über der Diphtherie-herztod und dessen Beziehungen zum Reizleitungssystem, Ztschr. f. Exper. Path. u. Therap. **11**:426, 1912. McCulloch, H.: Studies on the Effect of Diphtheria on the Heart, Am. J. Dis. Child. **20**:89 (Aug.) 1920. Smith, S. C.: Observations on the Heart in Diphtheria, J. A. M. A. **77**:765 (Sept. 3) 1921. Marvin, H. M.: The Effect of Diphtheria on the Cardiovascular System, Am. J. Dis. Child. **29**:433 (April) 1925.

after three negative cultures had been made. On October 10, thirty-three days after the onset of the diphtheria, he was admitted to the neurologic service with the following complaints: loss of voice, difficulty in walking, clumsiness in the use of the hands and the fingers, with tingling sensation and general weakness. The neurologic diagnosis was multiple neuritis following diphtheria. Because of an irregular pulse, electrocardiograms were made and ventricular extra systole,

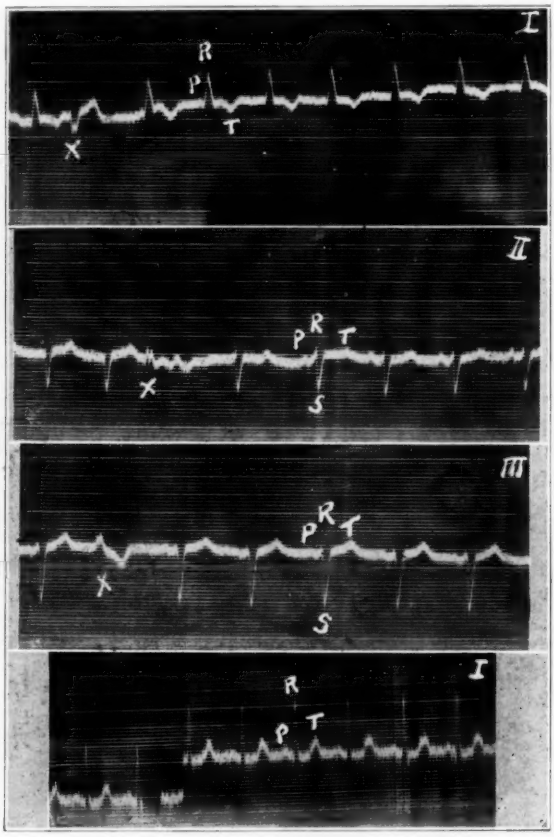

Chart 1 (case 1).—Leads I, II and III, and lead I (lowest record) three months later showing return to an upright T.

a left preponderance and an inversion of the T in lead 1 were revealed (chart 1). The patient was kept at rest in bed for three months, and at the end of that time showed a normal upright T in lead 1 (chart 1, lowest record).

Case 2.—M. B., a woman, aged 20, entered the contagious hospital on Oct. 13, 1925, with a history of sore throat, chills and fever, nausea and vomiting for four days. On examination she appeared toxic, the heart rate was rapid,

the uvula and tonsils were covered by a membrane, and the neck was swollen on both sides; the temperature was 103 F., and the pulse rate, 120. She received 20,000 units of antitoxin. On October 16, the membrane was shrinking and the general condition improved. Her course was satisfactory until October 20, seven days after admission. At 3:15 a. m. she suddenly complained of pain in the precordium, felt dizzy, vomited and looked pale. A slow pulse varying from 50 to 60 was noted. Stimulants were administered and the patient felt considerably improved during the day. On October 28, cultures of the throat were negative. Her progress had been satisfactory and she was allowed to sit up in bed. Her pulse rate, however, increased on even such slight exertion.

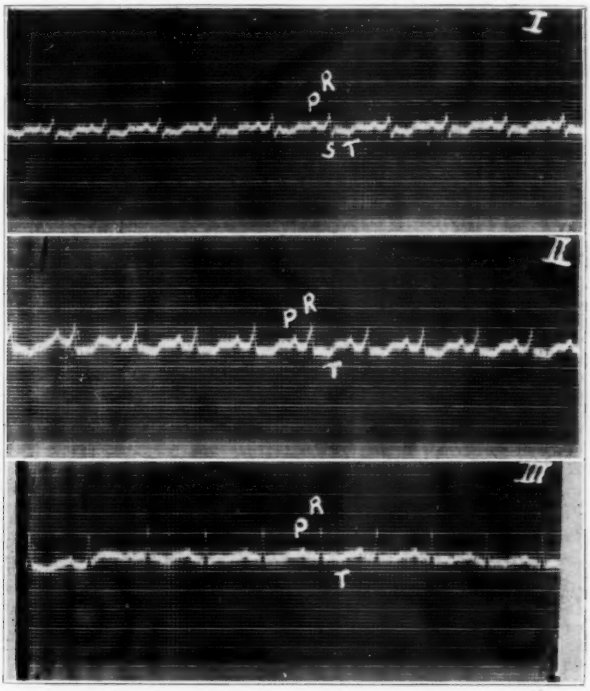

Chart 2 (case 2).—Leads I, II and III showing inverted T in all leads.

Physical examination on November 4 revealed a possible slight general dilatation of the heart, a gallop rhythm and an occasional extra systole. The impression was a probable mild degree of toxic myocardium. The following day the heart rate was 102 when the patient was resting and the blood pressure was 110 systolic and 70 diastolic. On November 4, an electrocardiogram was taken (chart 2) which showed inversion of the T in all leads with low voltage. On November 7, another electrocardiogram was taken which was essentially the same as the previous record. On November 11, the patient developed a numbness and peculiar tingling in the right hand and soft palate. On November 13, while sitting up in

bed and reaching for a pitcher of water, she suddenly gasped and fell back. A house doctor saw her at once. Her entire body was rigid, she was breathing in slow gasps; her pulse at the wrist could not be felt and the heart sounds could not be made out. She ceased breathing within a few minutes after the onset. An autopsy was not obtained.

Case 3.—V. H., a school boy, aged 12, entered the pediatric ward on Jan. 7, 1926, because of regurgitation of food through the nose. He gave the following history: On Dec. 3, 1925, he developed a sore throat, and on December 5, anti-

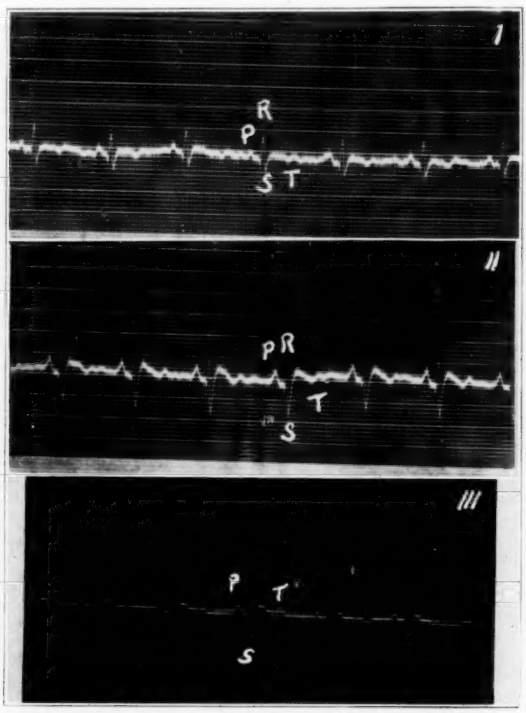

Chart 3 (case 3).—Leads I, II and III showing inversion of T_1 and T_2.

toxin was administered. The infection in the throat cleared up rapidly and he was allowed to be up and around by December 12. He felt weak, however, and tired easily and his mother noticed that his voice was peculiar. It was also noted at this time that there was a regurgitation of liquids through the nose. On examination, his heart was apparently normal with the exception that the rate increased easily on change of position. There was a moderate aphonia and the soft palate did not move on phonation. On January 15, an electrocardiogram (chart 3) showed inversion of the T in leads 1 and 2. The boy was kept in bed and his neurologic signs gradually disappeared. He was discharged on February 1. At this time the T wave was rather low, but had become upright. He returned to

the outpatient department on April 21 feeling well, and at the time an electrocardiographic tracing showed a well developed upright T wave in all leads (chart 4).

Case 4.—L. D., a child, aged 6, was admitted to the contagious hospital on Oct. 18, 1926, with a history of sore throat for one day, fever and vomiting. A large membrane was present over the tonsils and pharynx and there was a profuse nasal discharge. The temperature was 104 F., the pulse was rapid. The child appeared toxic. Twenty thousand units of antitoxin were administered. The child was seriously ill for ten days, but gradually improved and was discharged with three negative cultures on November 12. At this time an electrocardiogram showed a right preponderance with inversion of the T in leads 2 and 3

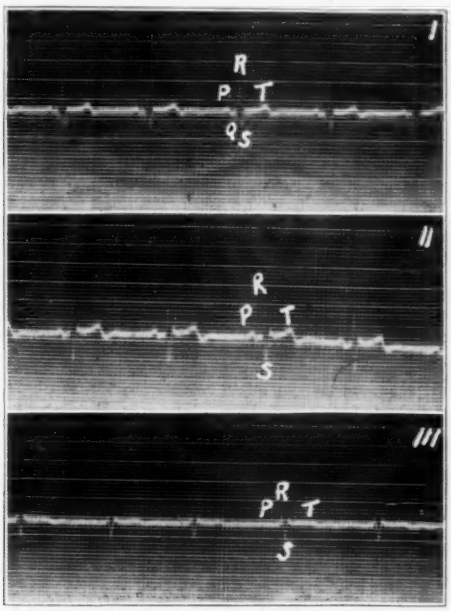

Chart 4 (case 3).—Well-developed, upright T; the electrocardiogram was taken three months after chart 3.

(chart 5). The mother was cautioned concerning the child's cardiac condition, and extreme restriction of activities was advised. Another electrocardiogram on Jan. 10, 1927, showed normal upright T waves (chart 6).

Case 5.—Mrs. M. H., aged 42, was admitted to the contagious hospital on Feb. 3, 1926, with the history that she had developed a sore throat three days previously, with swelling of the neck and hoarseness. On admission, her temperature was 100.8 F. and the pulse rate, 150. Her throat was markedly swollen, and there was marked edema of the soft palate and tonsillar tissues. There was a grayish exudate over the entire pharynx and tonsils, a brawny induration on

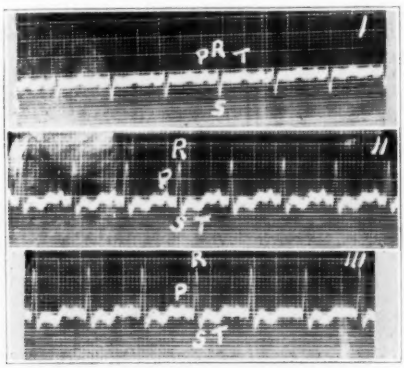

Chart 5 (case 4).—Leads I, II and III showing inversion of T_2 and T_3 in the fourth week.

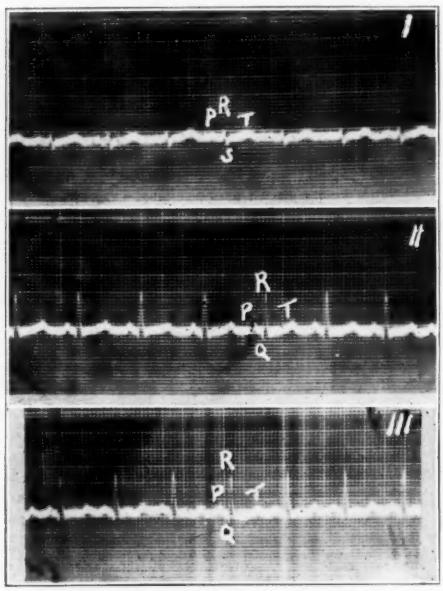

Chart 6 (case 4).—Normal upright T in all leads; taken two months after chart 5.

both sides of the neck; the heart tones and chest were normal. The patient was given 20,000 units of antitoxin intravenously. Because of her respiratory difficulty she was intubated. She had great difficulty in retaining the tube, and a tracheotomy was considered. She later coughed up a piece of membrane, and her breathing became easier. On February 15, 10,000 more units of antitoxin were given; the pulse rate was 150, and the patient looked seriously ill. On February 18, the membrane began to disappear and within a week it had entirely cleared up. An elevated temperature was present for about two weeks. On March 6, she developed a tonsillar abscess on the right side and later subcutaneous abscesses developed on the neck. She continued improving, however, and left the hospital on March 17. An electrocardiogram was taken on that day (chart 7) showing inversion of the T-1 and T-2. Three days after discharge from the hos-

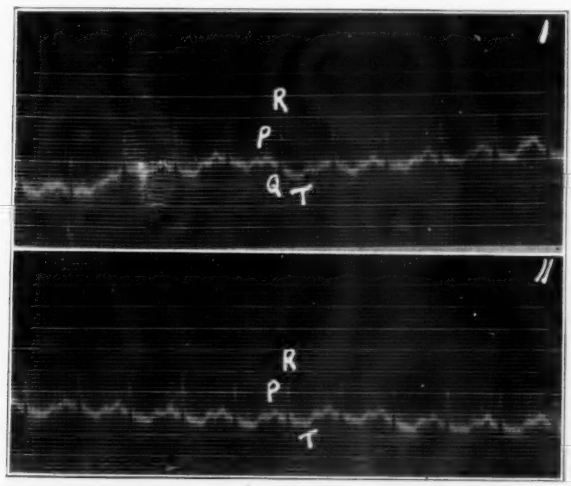

Chart 7 (case 5).—Leads I and II showing inversion of T in the eighth week of the disease.

pital, she developed difficulty in swallowing and regurgitation of fluids. Three days later, her difficulty in swallowing became more marked and she died suddenly during the afternoon.

CASE.—M. W., a woman, aged 24, noticed some soreness of her throat on Nov. 14, 1926. Her throat became swollen, and a physician was called who made a diagnosis of diphtheria, and she was admitted to the contagious hospital on November 16. She appeared toxic, with a pulse rate of 90, and temperature, 103 F. Thirty thousand units of antitoxin were administered intramuscularly. The fever was present only three days, and the patient gradually improved. On the eleventh day of her illness, she complained of some precordial pain, and on examination, a mild dilatation of the heart was considered probable. On November 29 an electrocardiogram showed an inverted T in leads 2 and 3 (chart 8). By December 1, she had shown three negative cultures. She showed a marked variation in pulse rate, however, and was transferred to the medical

service on December 9. On examination, her heart seemed slightly out to the left; the rate was 92, but auscultation revealed nothing abnormal. Electrocardiograms were taken several times a week, but did not show any change until Jan. 7, 1927, when the inverted T was replaced by an isoelectric T wave (chart 9). On December 22, she complained of some difficulty in swallowing. Some of the food appeared to stick in the upper part of the esophagus. The dysphagia gradually improved, but on January 6, she complained of some numbness in the lower extremities and also tingling in the hands and feet. On January 10, neurologic

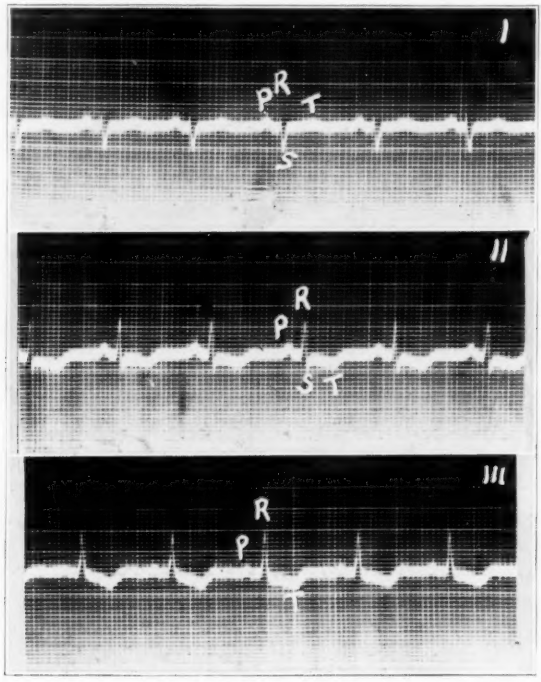

Chart 8 (case 6).—Inversions of T in leads II and III at the end of the second week.

examination showed the tendon reflexes present only on reinforcement and muscle power reduced in the lower extremities. The diagnosis was diphtheritic polyneuritis. These symptoms continued for several weeks and gradually cleared up. On January 21, the electrocardiogram showed low but upright T waves (charts 10); in subsequent tracings the T waves became more definitely positive. The patient was again seen on May 26, six and one-half months after the onset. She still complained of some weakness but of no definite symptoms suggestive of cardiac involvement. The physical examination was negative and the vital capacity was normal. An electrocardiogram showed upright T in all leads and the heart was normal in size on roentgen-ray examination.

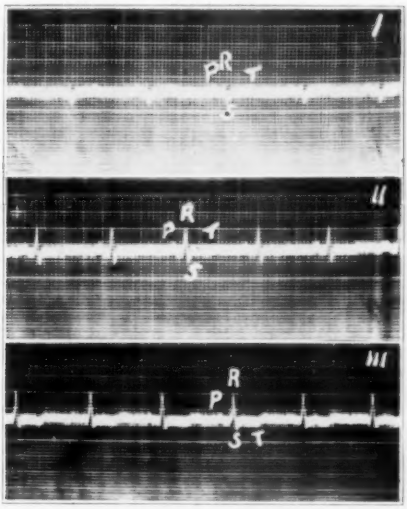

Chart 9 (case 6).—Five weeks after chart 8, showing iso-electric T in lead II.

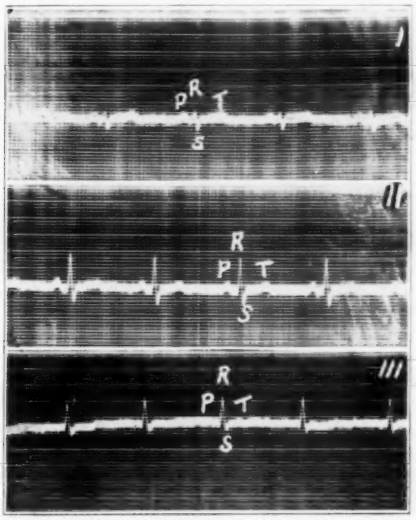

Chart 10 (case 6).—Two weeks after chart 9, showing definite upright T in lead II.

Case 7.—C. N., a man, aged 19, entered the contagious hospital on Oct. 1, 1926. He had complained of a mild sore throat for about a week but had been up and about. Three days before admission, his throat and general condition had become worse, and his neck began to swell on both sides. He was then seen by a physician and sent to the hospital. On admission, he appeared seriously ill, with a temperature of from 102 to 103 F.; the pulse rate was 110, and there was considerable difficulty in swallowing. There was a diphtheritic membrane in the throat, a profuse nasal discharge and a marked swelling on both sides of the neck. Thirty thousand units of antitoxin were administered. The patient's condition was serious for about two weeks. He was irrational at times, and apathetic and drowsy at other times. On October 11, he complained of extreme weakness, and became more

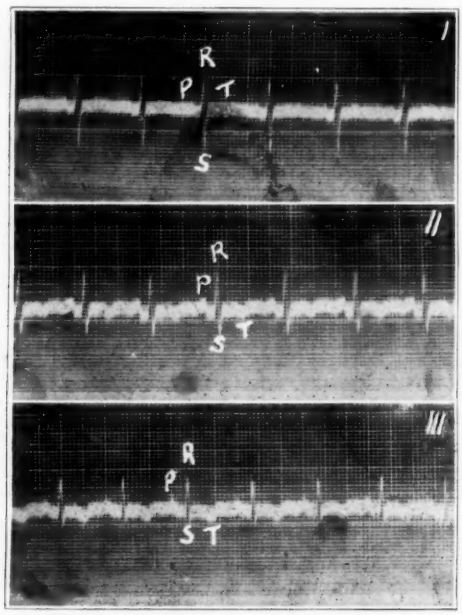

Chart 11 (case 7).—In sixth week of illness, showing inversion of T in leads II and III.

stuporous. Respiration was shallow and there was slight cyanosis of the fingers. The pulse rate was 60 and the temperature, 97 F. Two hundred and fifty cubic centimeters of 10 per cent dextrose were administered intravenously. Two days later his pulse rate was still slow, as low as 52. Respiration was shallow; his face was pale, and there was still some cyanosis of the fingers. His circulatory symptoms improved during the day. Following this his general condition gradually improved, but he developed a motoraphasia on October 20, from which he began to recover within two days. During this time he had been running a pulse rate of 60 or below. On October 26, his pulse rate was more rapid, being 72. After four negative cultures were obtained, he was transferred to the medical service on November 4 because of marked lability of the pulse. On examination, the

pulse at rest was found to be 88, the blood pressure was 134 diastolic and 78 systolic. Physical examination of the heart was negative. An electrocardiogram on November 5 showed inversion of T-2 and T-3 (chart 11). Electrocardiograms taken every three or four days did not show any change until November 19, when the T inversion was less marked in degree. On December 3, the T wave was positive but of low amplitude (charts 12). All of the subsequent electrocardiograms were normal.

An analysis of the electrocardiographic observations in these cases shows the following. There was an absence of high grade irregularities,

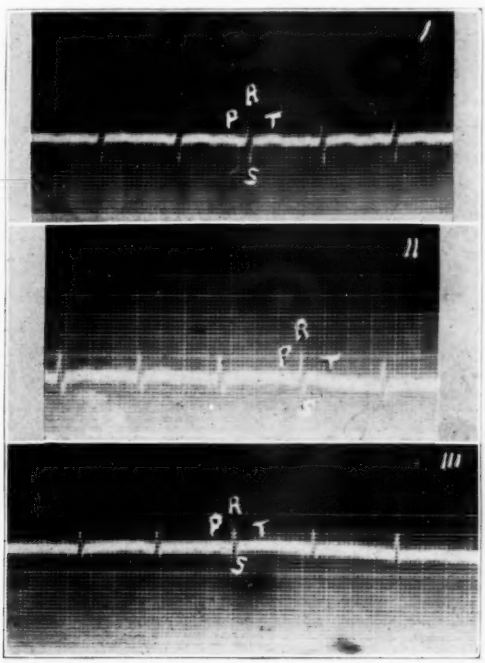

Chart 12 (case 7).—Four weeks after chart 11, showing low but upright T in leads II and III.

occasional ventricular extra systoles being the only arrhythmia noted in two cases. There was no evidence of prolonged auriculoventricular or intraventricular conduction time. The longest PR interval was 0.18 seconds and the QRS complex was not altered in any case. The chief significant change was in the T wave. A definite inversion of the T was present in all. In one instance, the T was inverted in lead 1 and in another in leads 1 and 2. In three cases, the change occurred in leads 2 and 3 and in two instances, in all leads. In addition, four

electrocardiograms showed a right preponderance and two a left preponderance. In two cases, sudden death occurred within a week after the readings were taken. The patients have recovered in the remaining five cases, and with recovery the T wave has become upright. The change was a gradual one, the T first becoming less negative, then iso-electric, and later, positive. The earliest evidence of return to normal was noted seven weeks after the onset of the disease. The return of the T wave to normal in the cases of patients who recovered is of interest. It is still believed by some that diphtheria is a cause of cardiac failure in later life. The foregoing observations strongly suggest that the effect is entirely a transient one, and that there is a restoration of normal myocardial function.

THE SIGNIFICANCE OF T WAVE INVERSION

It is generally accepted that the initial portion of the ventricular complex, the QRS, is a composite picture of a spread of the wave of excitation throughout both ventricles. The period between the S and T which usually is at the base line indicates that the entire muscle of the heart is in a state of excitation and therefore there is no difference in electropotential between its various portions. There is still some difference of opinion, however, as to the exact mechanism of the T deflection. The weight of evidence seems to indicate that the T is an electrical expression of the passing off of the excitation wave just as the QRS is a result of the spread of this process. The T wave exists because all portions of the ventricular muscle do not return to the resting electrical state uniformly and synchronously, thereby producing differences in the potential and thus a deflection of the galvanometer string. Normally, the T wave is upright and this is explained on the basis that the apex of the left ventricle returns to its resting state before the base of the right ventricle. It would seem justifiable then to consider an inverted T as an indication of an abnormal retreat of the excitation process in which the apical portions remain in a state of excitation longer than the base.

Experimentally, alterations in the T wave have been produced in various ways, and many of these observations lend support to this conception of the mechanism of the T wave. In frogs, Mines [2] has demonstrated that on local warming of the apex the T, if inverted will become upright, while if it is positive it will become still more positive. Smith [3]

2. Mines, J. R.: On the Functional Analysis by the Action of Electrolytes, J. Physiol. **46**:188, 1913.

3. Smith, F. M.: Further Observations on the T wave of the Electrocardiogram of the Dog Following the Ligation of the Coronary Arteries, Arch. Int. Med. **25**:673 (June) 1920.

has observed that cooling the apex of the left ventricle of dogs with ethyl chloride spray results in inversion of the T, while the change was of a lesser degree on cooling the middle anterior surface of the left ventricle. Disturbance of the blood supply to the left ventricle by ligating the ramus descendens and circumflex arteries is followed shortly by deep inversion of the T wave. Smith interpreted his results after coronary ligation and cooling of the apex as due to prolongation of the excitation at the apex which has been damaged by these procedures. Hamburger [4] and his associates have shown that T wave inversion occurs in dogs following experimental embolism from injection of a suspension of *Lycopodium* spores into the coronary circulation.

It is also well known that the introduction of certain substances affect the T wave. In experimental animals and in human beings, digitalis in sufficient dosage will flatten and invert the T wave.[5] In dogs and cats, ether narcosis may produce a similar effect.[6] Several observers have studied the effects of nerve stimulation on the form of the ventricular complex. In frogs, Samojloff [7] found on stimulation of the vagus nerve, inversion of the T wave if it was positive, and if negative it became more strongly so. Dale and Mines [8] noted that this type of alteration was not constant and at times the T became more markedly positive, while at others, it was entirely unaffected by stimulation of the vagus nerve. When Einthoven [9] stimulated the vagus nerves of dogs sufficiently to produce marked changes in the P wave and PR interval, he did not find any appreciable variation in the T wave. His observations suggest that in the mammalian heart nerve influences can play a minor part in affecting the T wave.

In the electrocardiogram of human beings, the T wave is found inverted normally with considerable frequency in lead 3. Alterations of the T in leads 1 and 2 are considered of definite significance, however, and there is great doubt whether such a condition ever occurs in the

4. Hamburger, W. W.; Priest, W. S., and Bettman, R. B.: Experimental Coronary Embolism, Am. J. M. Sc. **171**:168, 1926.

5. Cohn, A. E.; Fraser, F. R., and Jamieson, R. A.: The Influence of Digitalis on the T Wave of the Human Electrocardiogram, J. Exper. Med. **21**:593, 1915.

6. Miller, H. R.; Felberbaum, D., and Krigel, H. T.: Electrocardiographic Studies of the Effects of Ether upon the Living Cat's Normal Heart, Am. J. M. Sc. **169**:516, 1925.

7. Samojloff, A.: Weitere Beitrage zur Electrophysiologie des Herzens, Arch. f. d. ges. Physiol. **135**:417, 1910.

8. Dale, D., and Mines, G. R.: The Influence of Nerve Stimulation on the Electrocardiogram, J. Physiol. **46**:319, 1913.

9. Einthoven, W., and Wieringa, J. H.: Ungleichartige Vaguswirkungen auf das Herz, Electrocardiographisch untersucht, Arch. f. d. ges. Physiol. **149**:48, 1912.

normal heart. Lewis [10] stated that normally a negative T is never found in leads 1 and 2. In a recent book on electrocardiography, Weber [11] said that the inversion of the T wave in the first two leads must always be considered pathologic. Ferguson and O'Connell [12] recently made an electrocardiographic study of 1,812 midshipmen at the Naval Academy This material consisted of a group of healthy young adults in whom cardiovascular pathologic processes had been excluded by the usual methods. There were no records showing inversion of the T in lead 1. In only eight cases, or less than 0.5 per cent of the total number, a negative, iso-electric or diphasic T-2 associated with a negative T-3 was noted. In view of the fact that only a portion of these cases were true inversions, and that a second record showed a return to normal, this report confirms the general conception that the inversion of T-1 and T-2 is rarely if ever found in the absence of pathologic processes. Furthermore, one is strongly impressed with the almost constant association of the T wave inversion with serious cardiac disease. The pathologic conditions under which T wave changes are most frequently found are the chronic diseases of the myocardium associated with hypertension and coronary artery disease. In the enlarged heart in cases of hypertension, the T wave inversion is usually associated with a left ventricular preponderance. In disease of the coronary arteries, Pardee [13] and Willius and Brown [14] found T alterations in from 60 to 70 per cent of the cases. In chronic valvular disease, changes in the form of the ventricular complex occur with much less frequency. From extensive statistical studies in all types of cardiac pathologic processes, Willius [15] demonstrated the serious prognostic significance associated with inversion of the T wave in the first two leads. Compared with a control group, patients showing this abnormality had a much shorter life expectancy, approximately 60 per cent dying of heart failure within a year. Changes of the T wave in the direction of negativity have been noted with myxedema. Fahr [16] and Thatcher and White [17] described a low and

10. Lewis, T.: Clinical Electrocardiography, ed. 3, London, Shaw & Company, 1924, p. 36.

11. Weber, A.: Die Electrokardiographie, Berlin, Julius Springer, 1926, p. 113.

12. Ferguson, D., and O'Connell, J. T.: Cardio-Vascular Observations, U. S. Nav. M. Bull. **24**:860, 1926.

13. Pardee, H. E. B.: Heart Disease and Abnormal Electrocardiograms, Am. J. M. Sc. **169**:270, 1925.

14. Willius, F. A., and Brown, G. E.: Coronary Sclerosis, Am. J. M. Sc. **168**:165, 1924.

15. Willius, F. A.: Electrocardiography and Prognosis, Arch. Int. Med. **30**:434 (Oct.) 1922.

16. Fahr, G.: Myxedema Heart, J. A. M. A. **84**:345 (Jan. 31) 1925.

17. Thacher, C., and White, P. D.: Electrocardiograms in Myxedema, Am. J. M. Sc. **171**:61, 1926.

slightly inverted T which increased in amplitude in the positive direction after the administration of thyroid. Wood and White [18] observed T wave inversion in uremia with high nitrogen retention, and they believe that this is due to a toxic effect on the heart muscle. Electrocardiographic studies have also been carried out in some of the infectious diseases. The chief toxic effect observed in these is prolongation of the auriculoventricular conduction, seen most notably in cases of acute rheumatic fever,[19] but also in cases of influenza, pneumonia and

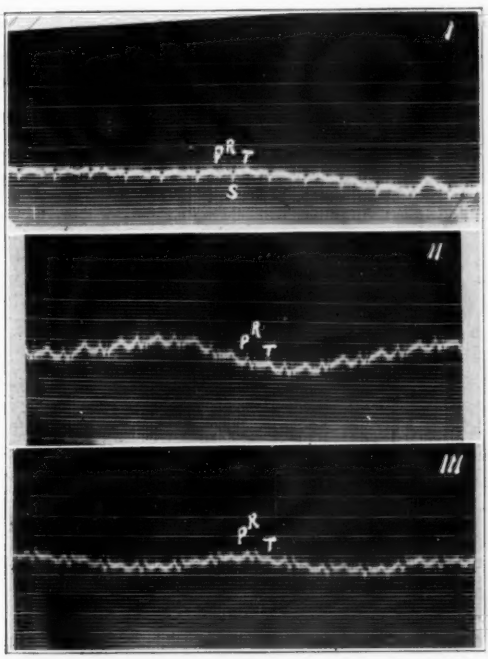

Chart 13.—Electrocardiogram of cat 2, before the injection of diphtheria toxin.

typhoid fever. Rothschild, Sachs and Libman,[20] in a recent report, described an abnormal ST portion of the ventricular complex in rheumatic fever, but no significant changes in the T wave.

18. Wood, J. E., and White, P. D.: The Electrocardiogram in Uremia and Severe Chronic Nephritis with Nitrogen Retention, Am. J. M. Sc. **169**:76, 1925.

19. Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, J. Exper. Med. **39**:1, 1924.

20. Rothschild, M. A.; Sachs, B., and Libman, E.: The Disturbances of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, Am. Heart J. **2**:356, 1927.

One may conclude from the foregoing physiologic and clinical observations that: (1) T wave inversion is probably an expression of an abnormal dying away of the excitation process and may be produced experimentally by injury to the myocardium, especially to the apex of the left ventricle, and that (2) this electrocardiographic abnormality is usually associated with cardiac pathologic processes of a serious nature. The present observations during the period of convalescence in cases of diphtheria suggest strongly that a bacterial toxin may so affect the

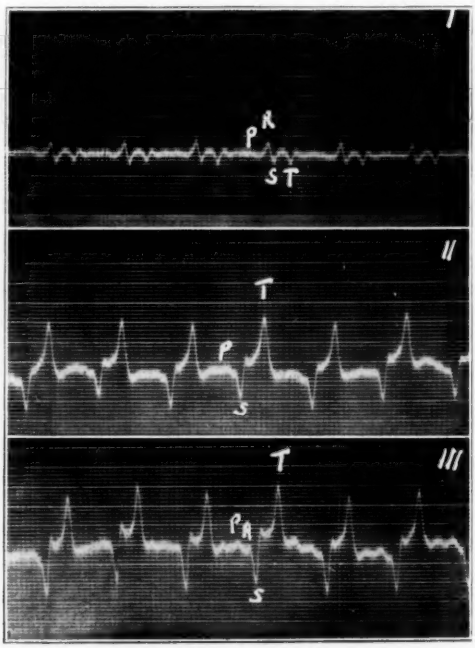

Chart 14.—Electrocardiogram of cat 2, showing widening of QRS and inversion of T in lead I, forty-eight hours after injection of diphtheria toxin.

passing off of excitation that a negative T wave results. Thus it would seem justifiable to conclude that T wave inversion in addition to its previously accepted significance may also indicate an injury to the heart muscle by a bacterial toxin.

OBSERVATIONS ON EXPERIMENTAL DIPHTHERIA TOXEMIA

An attempt was made further to confirm this by a study of the effects of diphtheria toxin in experimental animals. In the course of an investigation on the problem of whether diphtheria toxin possessed

any special affinity for the conducting tissue of the heart, Rohmer [21] injected diphtheria toxin into four rabbits. In a brief paragraph, he merely stated that he did not find any evidence of delayed conduction. He did not refer to any other changes. This seems to be the only previous report on the use of the string galvanometer in the study of experimentally produced diphtheria.

Cats were used in the present study, and diphtheria toxin [22] was injected subcutaneously. The dose of toxin varied from 0.03 to 0.05 cc.

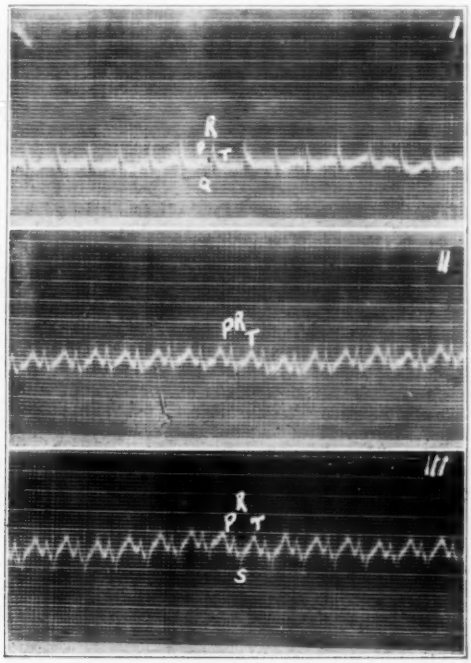

Chart 15.—Electrocardiogram of cat 3, before the injection of diphtheria toxin.

diluted to 2.5 cc. in sterile saline. The records were taken with the animal under light ether anesthesia. After a control record was taken and the toxin injected, subsequent readings were made at forty-eight hours and at varying intervals following this, if the animals remained alive. All the animals exhibited definite evidence of intoxication. The effect was usually noted on the second day following the injection. The

21. Rohmer (footnote 1, first reference).

22. The toxin was supplied by Dr. W. P. Larson of the Department of Bacteriology. A minimum lethal dose equals 0.4 cc.

animals became apathetic, moved about little and refused their food. Only a small amount of anesthetic was necessary in taking the subsequent readings as they offered but slight resistance. A frequent observation was weakness and stiffness of the hind legs. This usually occurred on the second or third day.

Of ten satisfactory experiments, electrocardiographic changes were observed in eight after the injection of the toxin. These may be sum-

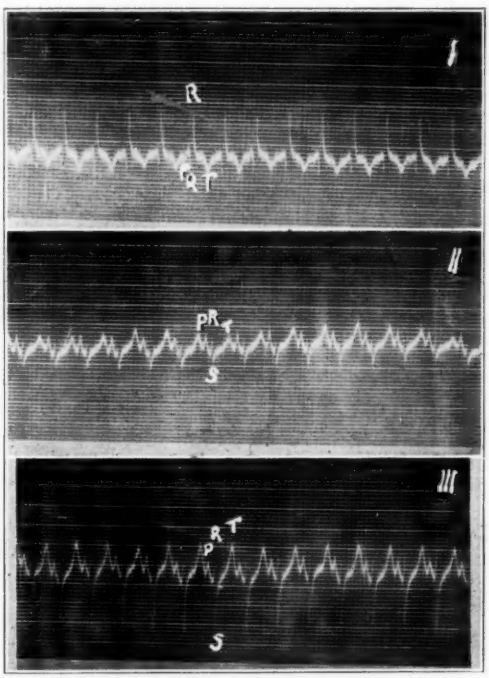

Chart 16.—Electrocardiogram of cat 3, forty-eight hours after injection of diphtheria toxin showing inversion of T in lead I and left ventricular preponderance.

marized as follows. Definite arrhythmia did not occur. Definite changes in the PR interval and QRS complex were present in but two cases. In one animal, six hours before death, the record showed a PR interval of 0.12 second, where it had previously been 0.06 second. At the same time, the QRS had markedly increased in amplitude and had widened from 0.02 to 0.06 seconds. The tracing was of a type indicating a bundle branch block. In another instance a similar record, but with changes of lesser degree, was noted at forty-eight hours. The most

constant and striking alterations were in the T wave. There was definite flattening and inversion of the T wave in one or more leads in all cases, as early as forty-eight hours following the injection of the toxin. The change was present in lead 1 alone, in three cats, and in leads 1 and 2 in one animal. In the remaining four, the inversion was present in leads 2 and 3. In two cats in whom it was possible to follow results for seven and ten days, a tendency for return of the T to normal appeared between the third and sixth day in one instance, and between

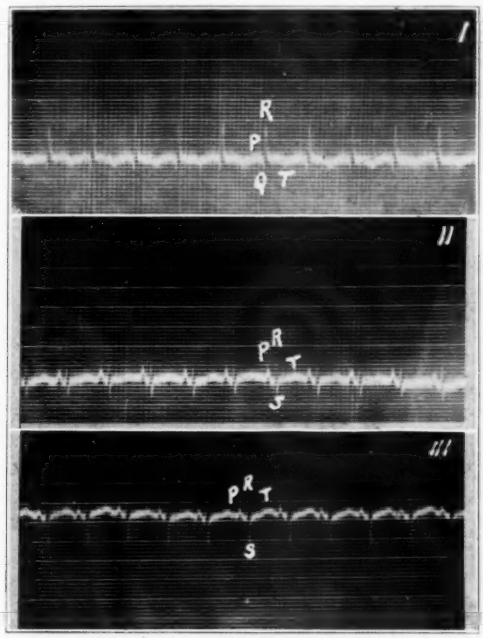

Chart 17.—Electrocardiogram of cat 3, showing partial return to normal of T in lead I, four days after chart 16.

the fifth and eighth day in the other. In addition, in two animals there was a definite change in ventricular preponderance, both within forty-eight hours, following the injection of toxin. In both cases a definite left ventricular preponderance developed.

Similar rapid changes in preponderance are reported by McCulloch [23] and Marvin [24] in their clinical cases. In one case, a definite flaccid paralysis of the hind extremities was present on the tenth day, when the

23. McCulloch (footnote 1, second reference).

24. Marvin (footnote 1, fourth reference).

electrocardiographic changes were returning to normal. This is of interest since clinically diphtheritic paralysis and circulatory failure are often associated, and attempts have been made to explain both on a nervous mechanism. This experiment shows paralysis occurring at a time when there is evidence of recovery in the heart.

COMMENT

Electrocardiographic observations carried out on a series of patients with diphtheria during convalescence, and on cats given diphtheria toxin, show evidence of a definite damage to the myocardium. These observations have some theoretical and practical application. First, they have a bearing on the question of the mechanism of the circulatory failure in diphtheria. Various investigators have noted a progressive drop in blood pressure ending in death after the production of diphtheria toxemia in animals. As already mentioned, there is a difference of opinion as to whether the seat of circulatory insufficiency lies in the heart or in the vasomotor apparatus.

In 1899, Romberg and his associates [25] carried out an extensive series of experiments on the circulatory mechanism in infections. Following this it was generally accepted that diphtheria toxin produces a paralysis of the vasomotor center with loss of vasomotor control of the arteries, allowing them to relax so that the circulation fails. The observations of MacCallum,[26] using different experimental methods, seemed to confirm Romberg's conclusions. Porter and Pratt,[27] on the other hand, concluded that the vasomotor center was unimpaired by diphtheria toxin. Pathologists, pointing out the extensive degenerative changes which may occur in the heart in diphtheria, insist that the myocardial weakness is the essential factor in the circulatory failure. In a recent report, Warthin [28] presented an excellent review of the entire subject including a pathologic study of the heart in a group of cases. He concluded that the myocardium shows a characteristic pathologic picture in diphtheria and that the essential lesion is a "toxic parenchymatous hyaline degeneration or necrosis frequently associated with fatty degenerative infiltration and less frequently with cloudy

25. Romberg, E.; Passler, H.; Bruhns, C., and Muller, W.: Untersuchungen über die allgemeine Pathologie und Therapie der Kreislaufstörung bei acuten Infectionskrankheiten, Deutsches Arch. f. klin. Med. **64**:652, 1899.

26. MacCallum, W. G.: The Mechanism of Circulatory Failure in Diphtheria, Am. J. M. Sc. **147**:37, 1914.

27. Porter, W. T., and Pratt, J. H.: The State of the Vasomotor Centre in Diphtheria Intoxication, Am. J. Physiol. **33**:431, 1914.

28. Warthin, A. S.: The Myocardial Lesions of Diphtheria, J. Infect. Dis. **35**:32, 1924.

swelling or simple necrosis." In a study of nineteen cases, Loth [29] was unable to demonstrate any specific myocardial lesion and stated that the changes observed were merely cloudy swelling or fat infiltration such as occurs in other acute infections. MacCallum [30] does not believe that the structural changes observed impair the function of the heart sufficiently to explain the disturbances in circulation. There are other observers also who maintain that the pathologic conditions in the heart do not offer convincing evidence of the cause of death. One may conclude therefore, that although pathologic studies favor the myocardial theory, they do not permit a final conclusion as to the exact part played by the heart muscle. This is not surprising in view of the fact that it is difficult with the present knowledge to correlate disturbances in myocardial function with structural changes in the heart. The electrocardiographic changes noted by Smith,[31] McCulloch [32] and Marvin [33] during the acute stages, and those described in the present report during convalescence, are of a type which is usually found associated with serious cardiac disease in which myocardial function is definitely impaired. It would not be possible to explain these significant electrocardiographic changes by any vasomotor mechanism. These observations therefore offer additional evidence in favor of a myocardial basis for the circulatory failure in diphtheria.

Another of the various theories for the sudden collapse during the period of convalescence in cases of diphtheria is that it is due to a toxic injury of the vagus nerve. This has been suggested because of the well-known fact that diphtheria toxin has a special affinity for nerve tissue, and also for the reason that the circulatory collapse occurs most frequently in cases showing signs of nerve disturbance. It will be noted that six of the seven cases showed some evidence of involvement of the nerves. In most instances, this was mild in character and did not seem to bear any relationship to the extent of myocardial damage. Case 1, for example, with evidence of severe injury to the nerve ended with recovery, while case 2, with mild neurologic symptoms, terminated in death. Furthermore, in the entire group of fifteen cases there were several in which there was definite paralysis of the soft palate in which the electrocardiograms were normal. It is also of some significance that there was no correspondence in time of onset of the electrocardiographic change and the evidence of nerve disturbance. Case 6, which showed

29. Loth, M.: The Heart in Diphtheria, Arch. Int. Med. **31**:637 (May) 1923.

30. MacCallum, W. G.: A Text-Book of Pathology, Philadelphia, W. B. Saunders Company, 1924, p. 465.

31. Smith (footnote 1, third reference).

32. McCulloch (footnote 1, second reference).

33. Marvin (footnote 1, fourth reference).

inversion of the T on November 29, first gave evidence of return to normal on January 7 with a flat iso-electric T wave, at a time when the neurologic signs were most marked. Similarly case 7 began to show evidence of involvement of the nerve after the T wave had become upright. A similar condition occurred in one of the animals that developed a definite flaccid paralysis of the hind extremities on the tenth day when the electrocardiographic changes were returning to normal. As already mentioned, T inversion has been experimentally produced in some animals by stimulation of the vagus nerve, although Einthoven's observations on dogs indicate that such an effect is extremely unlikely in the human heart. In an attempt to ascertain whether stimulation of the vagus nerve could be playing any part in the T inversion, cases 6 and 7 were studied after the injection of atropine sulphate. This was done at a time when the T wave inversion was definite. Atropine sulphate, 0.002, was injected subcutaneously, and several tracings were taken at intervals of ten minutes following the injection. Although there was marked dryness of the mouth and increased pulse rate, no change was noted in the amplitude of the T. These observations suggest that neither the circulatory disturbance nor the electrocardiographic alterations can be explained on the basis of a nerve injury by diphtheria toxin.

Among those who accept the presence of a myocardial injury in diphtheria there is still a difference of opinion as to the duration of this involvement and its later significance. For example, Schwensen [34] considers diphtheria as an important cause of chronic cardiac disease later in life. McCulloch,[35] in his conclusions, stated that "myocarditis due to diphtheria has a definite position among the factors that lead to chronic heart failure later in life." On the other hand, Place [36] said that he has never found evidence of fibrous myocarditis following diphtheria. The return of the T wave to normal in the cases of this group in which recovery occurred suggested a restoration of the myocardium to a normal state. The indications are, therefore, that the toxic effect is a transient one and that it is improbable that diphtheria is a factor in chronic disease of the myocardium. In case 6, in which examination was made six and one-half months after the onset, the physical condition of the heart and the vital capacity of the lungs, were normal, as was the electrocardiogram, and there was no evidence of dilatation in a roentgenogram of the heart made at a distance of 6 feet.

34. Schwensen, C.: The Heart Rhythm in Diphtheria, J. Infect. Dis. **30**:279, 1922.

35. McCulloch (footnote 1, second reference).

36. Place, E. H.: Oxford Medicine, vol. 5, p. 148.

PRACTICAL APPLICATIONS

Although it is generally agreed that involvement of the circulation following diphtheria is of serious import, there is no accurate clinical method for detecting its presence. The late circulatory collapse may come on without warning. The physical examination usually gives no hint of the presence of a serious condition and blood pressure studies do not offer any assistance. Rolleston,[37] for instance, stated that blood pressure readings are of little practical value. The present study of the seven patients showing positive electrocardiographic evidence reveals no reliable clinical signs or symptoms by which myocardial involvement may have been suspected. It is true that an irritability of the heart existed, but this is a frequent occurrence in a variety of conditions and is of no value as an indication of myocardial injury. In the physical examination in several instances, there was a transient occurrence of extra systoles and alterations in tone with gallop rhythm. Neither of these is diagnostic of myocardial damage. Some degree of dilatation of the heart is undoubtedly present, and this has been shown by the roentgen-ray studies of Dieteln [38] and Dorner.[39] The degree of dilatation, however, is such that it would be rather difficult of recognition by the ordinary clinical methods. There was no evidence of gross dilatation in any of the seven cases. Furthermore, when myocardial involvement is suspected, there is no means of knowing the duration of such involvement. This is of considerable importance. From a large experience in contagious diseases, Place [36] emphasizes the value of sufficient absolute rest until the evidence of involvement of the heart muscle has disappeared. He stated that in his experience, late death does not occur if the patient is kept at rest for a suitable period. It would seem justifiable, therefore, whenever it is possible to make an electrocardiographic study of the patient with diphtheria during the convalescent period. If inversion of the T wave is found, extreme restriction should be carried out until there is a restoration of the normal upright T wave.

CONCLUSIONS

1. In fifteen severe and moderately severe cases of diphtheria, approximately 50 per cent of the patients showed inversion of the T wave in significant leads during convalescence.

2. Two patients showing inversion of the T died suddenly.

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37. Rolleston, J. D.: Acute Infectious Diseases, New York, Phys. & Surg. Book Company, 1925, p. 30.

38. Dieteln, H.: Ueber Herzdilatation bei Diphtherie, München. med. Wchnschr. **52**:683, 1905.

39. Dorner, J.: Clinical Studies in the Pathology and Treatment of Diphtheria, Jena, Gustav Fischer, 1918, p. 136.

3. In the patients that recovered, the inverted T wave returned to normal as early as seven weeks after the onset of the disease.

4. Cats injected with sublethal doses of diphtheria toxin showed consistently similar T wave alterations, usually within forty-eight hours.

5. These observations support the myocardial theory of the circulatory failure in diphtheria.

6. Electrocardiographic studies are of practical value in diphtheria during the period of convalescence, to ascertain both the presence of myocardial involvement and its duration.

ADDENDUM

Since the writing of this paper, the following case has come under observation:

E. M., a man, aged 37, was admitted to the General Hospital on Nov. 2, 1927, with the following complaints: marked weakness, difficulty in swallowing, disturbance in speech, diplopia and numbness over the entire body. About three weeks before admission the patient noticed weakness of his upper and lower extremities accompanied by a feeling of numbness. He also noticed that his vision became blurred. About two weeks before entering the hospital, he was forced to discontinue his work because of inability to walk. At this time he began having difficulty in swallowing so that he choked on eating solid food and liquids frequently regurgitated through the nose. At present he is unable to swallow anything unless he is in the upright position. He is unable to speak clearly, and there is a nasal quality to the voice. He has also noted that in washing his face, he cannot distinguish between warm and cold water.

Physical examination showed marked evidence of polyneuritis. There was inability to converge with the eyes and inconstant diplopia in looking at far objects. The soft palate did not show any response to touch. Liquids regurgitated through the nose. In addition, there was a marked muscular weakness in all the extremities with an absence of tendon reflexes. There was no response to plantar stimulation, and position sense was absent in the extremities. Diagnosis by a neurologic consultant was that of advanced polyneuritis, probably due to diphtheria. On further questioning, the patient gave a history of having suffered a severe sore throat about four weeks previous to the onset of the present symptoms. He had consulted a physician, who had painted his throat daily. His left tonsil was also incised but pus was not obtained. He did not stop his work during the entire period, and was not given antitoxin, as a diagnosis of diphtheria was not made. As myocardial involvement is so frequently associated with diphtheritic neuritis, an electrocardiogram was taken which showed definite inversion of the T wave in lead 1 and a left ventricular preponderance. This was repeated, and showed the same changes. The patient's condition remained about the same until November 11, nine days after admission, when he seemed weaker, became short of breath, and râles were heard in the chest. Two days later, his pulse rate increased to 124, respiration to 42, and he was dyspneic. Five hours later, examination reavealed a pulse rate of 142, respiration, 42, and the heart sounds were fetal in character. One hour later, he was found dead in bed.

BASAL METABOLISM

III. INFLUENCE OF WORK WITH SPECIAL REFERENCE TO THE THYROID GLAND *

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The rise in metabolism due to work is well known.[1] Boothby and Sandiford [2] found that patients with exophthalmic goiter and adenomatous goiter with hyperthyroidism require nearly twice as much energy for a given piece of work as do normal persons or even patients with other diseases. A comparison of the basal metabolism and the metabolism as influenced by work in a series of fifty subjects is herein reported.

MATERIAL AND TECHNIC

The subjects were of three main groups: (*a*) normal persons (pupil nurses), thirteen; (*b*) patients clinically considered subjects of exophthalmic goiter or toxic adenoma, fifteen, and (*c*) other patients, twenty-two.

The basal metabolic rate is determined by indirect calorimetry, measuring the consumption of oxygen. The apparatus is provided with a drum which revolves in eight minutes. During the first five minutes, the technic does not vary from the routine except that explanation is first made of what the subject is asked to do during the last three minutes, and the rope handles to be described lie within his easy grasp, adjusted to his arms' length.

The effect of work is determined during the last three minutes, during which the subject lifts a weight equivalent to one-twelfth the body weight. The load is imposed by placing scales at the foot of the bed, putting on the scales ample weight of indifferent material in a box, balancing the scales, then setting back on the scale bar the "runner" a distance equivalent to one-twelfth the subject's weight. Attached to the weighted box and passing over the foot of the bed are two ropes with handles. At the end of five minutes, the subject is asked to make traction on the ropes just sufficient to maintain the scales in balance with the runner adjusted as described. The results are shown in the table.

Before considering the relation of the basal rate to the work rate, I shall refer to six cases (14, 16, 30, 36, 37 and 40) in which there was incomplete agreement between the basal rate and part of the clinical or pathologic evidence. In case 14, the pathologic report of mild toxicity was not supported by other evidence. In cases 16, 37 and 40, the patients are believed to have shown lower basal rates than they would have done except for previous recent treatment by the roentgen-ray, compound solution of iodine or both. The patient in case 30 had

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* From the Medical Service of St. Luke's Hospital.

1. Lusk, G.: Science of Nutrition, Philadelphia, 1923, p. 310.

2. Boothby, W. M., and Sandiford, I: Basal Metabolism, Physiol. Rev. **4**:95, 1924.

Data Relating to Subjects Included in the Study

No.	Date, 1927	Name	Age	Sex	Basal Metabolic Rate	M. R. with Load	M. R. with Load Less B.M.R.	Goiter	Previous Treatment	Clinical Diagnosis	Thyroid Treatment	Pathologic Diagonsis
1	Mar. 18	S. S.	19	F	+10	+22	12	0	.....	Normal		
2,A	Mar. 23	S. H.	20	F	— 6	+22	28	0	.....	Normal		
3	Mar. 24	P. E.	22	F	+ 8	+22	14	0	.....	Normal		
4	Mar. 25	W. S.	23	F	+16	+32	16	0	.....	Normal		
5	Mar. 29	R. N.	24	F	+12	+24	12	0	.....	Normal		
6, A	Mar. 31	W. N.	23	F	— 8	+30	38	0	.....	Normal		
7	April 4	E. S.	20	F	+ 8	+20	12	0	.....	Normal		
8	April 4	M. N.	23	F	+14	+24	10	0	.....	Normal		
9	April 5	F. X.	24	F	+ 4	+12	8	0	.....	Normal		
10	April 13	N. L.	45	M	+38	+62	24	+	.....	Chronic infectious tonsillitis, exophthalmic goiter	Tonsillectomy, roentgen ray	
11	April 14	A. D.	38	F	+10	+22	12	0	Thyroid extract	Myxedema	Thyroid extract	
12	April 15	O. C.	40	M	+42	+100	58	+	Compound solution of iodine	Exophthalmic goiter	Thyroidectomy	Exophthalmic goiter "mild"
13	April 30	J. W.	13	F	+15	+34	19	0	Thyroid extract	Hypothyroidism	Thyroid extract	
14*	April 30	H. P.	46	M	— 4	+ 4	8	+	.....	Cystic goiter	Thyroidectomy	Adenoma cystic, mildly toxic
15	April 30	N. H.	42	F	— 2	+10	12	0	.....	Ovarian cyst		
16,A*	May 5	D. S.	29	F	+ 5	+42	37	+	Six roentgen-ray exposures 6 months before; compound solution of iodine ?	Nontoxic adenoma*	Thyroidectomy	Toxic adenoma (hemorrhagic)
17	May 7	N. V.	38	F	+56	+80	24	+	.....	Exophthalmic goiter	Thyroidectomy	Adenoma in exophthalmic goiter
18	May 9	S. F.	20	M	—25	— 6	19	0	.....	Hypothyroidism	Thyroid extract	
19	May 21	A. D.	25	F	—10	+10	20	+	.....	Dysmenorrhea	Thyroid extract	
20	May 23	E. T.	21	F	+56	+78	22	+	.....	Exophthalmic goiter	Thyroidectomy	Exophthalmic goiter
21	June 1	M. B.	36	F	+46	+84	38	+	.....	Exophthalmic goiter	Thyroidectomy	Exophthalmic goiter
22	June 8	McC.	52	F	+12	+22	10	+	.....	Thyroiditis, acute; chronic infectious tonsillitis		
23,B	June 10	B. Y.	48	F	+22	+28	6	0	Not basal	Chronic cystitis; chronic infectious tonsillitis	Tonsils removed	

24	June 13	G. P.	30	F	+60	+92	32	+	Compound solution of iodine	Toxic goiter	Thyroidectomy	Exophthalmic goiter
25	June 15	L. S.	23	F	+16	+18	2	0	.....	Normal		
26	June 15	B. R.	20	F	+ 8	+24	16	0	.....	Normal		
27	June 18	C. C.	48	M	+38	+88	50	+	.....	Exophthalmic goiter chronic infectious tonsillitis	Thyroidectomy; tonsils removed	Adenoma, colloid and exophthamic goiter
28	June 23	C. S.	22	F	− 2	+12	14	0	.....	Normal		
29	June 24	E. H.	41	F	+64	+88	24	+	.....	Pregnancy; toxic adenoma	Abortion; thyroidectomy	Toxic adenoma
30,B*	Sept. 30	M. C.	33	F	+33	+42	9	+	.....	Pulmonary tuberculosis; chronic psychosis; nontoxic adenoma	Thyroidectomy	Adenoma
31	Oct. 4	M. D.	43	F	+42	+70	28	0	.....	Exophthalmic goiter	Thyroidectomy	Active exophthalmic goiter
32,B	Oct. 5	L. W.	37	F	+22	+40	18	+	.....	Tuberculosis of thyroid	Thyroidectomy	Tuberculosis of thyroid
33	Oct. 5	N. W.	37	F	−16	+ 1	17	0	.....	Duodenal ulcer; chronic infectious tonsillitis		
34	Oct. 5	P. D.	50	F	− 6	+ 8	14	0	.....	Chronic cholecystitis and appendicitis		
35,A	Oct. 6	N. C.	50	F	± 0	+24	24	0	.....	Tachycardia; chronic infectious tonsillitis		
36,A*	Nov. 7	A. F.	51	F	+20	+48	28	0	.....	Diabetes; nontoxic adenoma		
37*	Nov. 8	J. W.	40	F	+18	+26	8	+	Roentgen ray, compound solution of iodine	Exophthalmic goiter	Thyroidectomy	Exophtralmic goiter
38	Nov. 10	M. J.	48	F	+19	+32	13	+	.....	Toxic adenoma	Thyroidectomy	Adenoma
39	Nov. 12	R. G.	20	F	−11	+ 4	15	"Not path."	.....	Patient's suspicion of goiter		
40,A*	Nov. 14	M. M.	42	F	+18	+40	22	+	Compound solution of iodine	Exophthalmic goiter	Thyroidectomy	Exophthalmic goiter
41	Nov. 14	R. M.	17	F	− 6	+10	16	"Full"	Thyroid extract	Myxedema	Thyroid extract	
42	Nov. 16	C. P.	27	F	− 7	+10	17	0	.....	Pyorrhea; nephrolithiasis		
43	Nov. 18	P. H.	67	F	+ 4	+20	16	0	.....	Cancer of uterus		
44	Nov. 18	L. H.	22	F	+ 2	+10	8	"Full"	.....	Chronic infectious tonsillitis, antrum and teeth		
45	Nov. 21	F. K.	35	F	− 7	+ 5	12	"Full"	.....	Slight simple goiter		
46	Nov. 22	R. F.	41	F	± 0	+15	15	0	Not basal	Normal		
47	Nov. 23	M. C.	22	F	−14	+ 1	15	+	.....	Simple goiter		
48	Nov. 28	D. D.	25	F	+32	+74	42	0	.....	Exophthalmic goiter	Thyroidectomy	Exophthalmic goiter
49	Nov. 28	E. H.	32	F	+52	+116	64	0	.....	Exophthalmic goiter	Thyroidectomy	Exophthalmic goiter
50	Nov. 30	L. F.	60	F	−12	− 3	9	0	.....	Pernicious anemia		

* In these cases there was incomplete agreement between the basal rate and part of the clinical or pathologic evidence.

pulmonary tuberculosis, was an inmate of a psychiatric institution and the single rate determination is not believed to be truly basal. In case 36, the patient had diabetes mellitus and an adenomatous thyroid gland believed to be nontoxic.[3]

The comparison between the basal rate and the rate induced by the load is best seen in the chart.

In plotting the chart, the basal rate is scaled on the base line and the rise in rate on a vertical line. It is to be noted that the difference between the basal rate and the work rate is plotted and not the percentage of the patient's normal to which the rate rose. The field is arbitrarily divided by heavy lines at plus 20 on the basal rate scale and 20 per

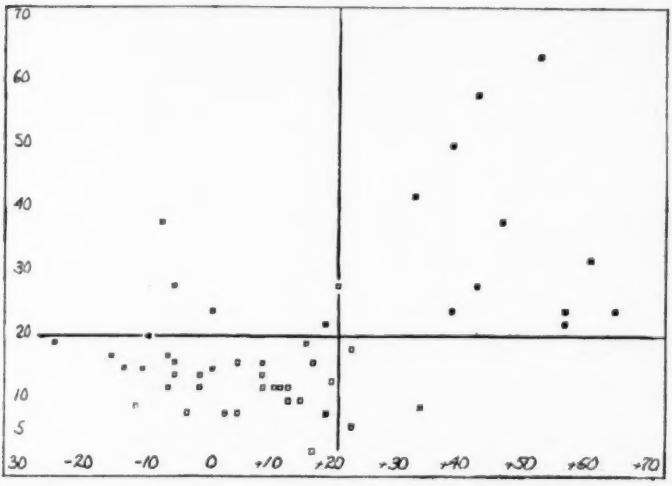

Chart showing comparison between the basal rate and the rate induced by the load. The basal rate is scaled on the base line and the rise in rate on the vertical line. The dark squares indicate results for patients with exophthalmic goiter or toxic adenoma; the light squares indicate results for other subjects.

cent rise on the work scale. Examination of the chart reveals a marked tendency for subjects with a basal rate of less than + 20 to show a rise under the load of less than 20 per cent of the subject's normal basal rate, and for those with a basal rate above + 20 to show a rise of more than 20 per cent. Of those conforming to the rule, there was only one subject with toxic goiter in the former group (southwest field), and all of the patients had toxic goiter in the latter (northeast field) group. The exceptions may be divided into two groups:

3. As determined by test reported Nov. 29, 1927; basal rate + 27, rate with load + 42, difference 15; pulse rate 80, 76 and 80 and temperature 99 F.

(*a*) those showing a basal rate of less than + 20, but a rise of more than 20 per cent (cases 2, 6, 16, 35, 36 and 40, marked A in the table), and (*b*) those showing a basal rate of more than + 20, but a rise of less than 20 per cent (cases 23, 30 and 32, marked B in the table).

Cases 16, 36 and 40 have been discussed. The patient in case 2, a "healthy" pupil nurse, had had diphtheria a year previous to the present illness; the throat had been troublesome since, and tonsillectomy was performed eight weeks after date of the test. In the patient in case 6, a "healthy" pupil nurse, active pulmonary tuberculosis was recognized six months after the test. The patient in case 35 had undergone the prolonged illness and death of her husband, a physician, and failure of economic efforts as keeper of a boarding-house, and had tachycardia and chronically infected tonsils.

Case 30 has been discussed. The patient in case 23 was selected as a nonbasal subject. The patient in case 32 had tuberculosis of the thyroid gland with many giant cells and an absence of typical thyroid hyperplasia.

The various modifying circumstances are not accorded great weight, since it is realized that their exact importance is unknown. They are mentioned, rather, as tending to justify the positive and negative conclusions regarding toxicity of the thyroid gland as shown in the chart.

COMMENT

It is not likely that determination of the basal rate as modified by work will find any wide usefulness as a diagnostic criterion. The limited data presented do not suggest that an abnormal rise due to work over a normal basal rate is specifically related to hyperfunction of the thyroid gland. Further investigation may establish the following tendencies:

A normal or borderline (+ 15 to + 25) rate rising abnormally under work may, in the individual subject, indicate that the thyroid gland pathologically is toxic, the rate being temporarily depressed under the influence of treatment.

A high basal rate not rising in the degree usually associated with toxic goiter may indicate that the increased basal rate is not due to a pathologic thyroid gland or is not truly basal.

Aside from the influence of previous treatment, the series contains several borderline basal rates with a normal rise (cases 4, 8, 13, 23 and 25), but none of the cases was concluded to be toxic goiter, though the thyroid was diseased in two cases (38 and 32).

The subjects with subnormal basal rates appeared to respond to work with a rise as great or greater than those with basal rates between — 10 and + 15. This agrees with the observations of Boothby and Sandiford.

In this series, the extranormal cost of work of subjects with toxic goiter does not bear a constant ratio to their basal metabolic rate further than that it may be said the cost of work is higher than normal.

The average rise of rate in subjects with toxic goiter with basal rates above + 20 (12 cases) was 36.9 per cent, varying between 22 and 64 per cent.

The average rise in all others, including patients with toxic goiter with basal rates depressed by previous treatment (38 cases), was 14.1 per cent.

SUMMARY

In fifty subjects the basal metabolic rate was determined, followed by a determination of the rate as influenced by imposing a load of one-twelfth the subject's body weight. All subjects with toxic goiter and with abnormally high basal rates (twelve) showed an increase in rate under the load varying from 22 to 64 per cent of the subject's normal basal rate, and averaging 36.9 per cent. The average of thirty-eight other cases was 14.1 per cent.

Two of the three subjects with toxic goiter and with basal rates under plus 20 who were taking compound solution of iodine showed a rise under the load suggestive of the thyroid hyperfunctional state; one did not show any rise above the normal of 20 per cent.

In three cases in which the basal rates were above plus 20 and in which there was no rise above 20 per cent, none of the patients was found to have toxic goiter.

Of the subjects with borderline basal rates not showing a rise of more than 20 per cent, only the two patients taking compound solution of iodine were found to have toxic goiter.

No ratio appeared to exist between the increased basal rate of subjects with toxic thyroid and their abnormal response to work further than that the cost of work is higher than normal.

An increased response to work did not appear to be a specific thyroid toxic phenomenon.

CONCLUSION

Conclusions cannot be drawn from the limited data, but it is suggested that further investigation, possibly with improved technic, may demonstrate that the measured cost of work may be of aid in the diagnosis of toxic thyroid states in a limited number of cases in which the other data are confusing.

My thanks are due Miss Katie Gilliam, technician, for painstaking work in the rate determinations.

TOLERANCE FOR QUININE IN EXOPHTHALMIC GOITER

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About a decade ago, I began making observations on patients with exophthalmic goiter to determine their degree of tolerance to the ingestion of quinine. Part of the deductions derived were published in the nature of a description of the quinine test [1] for patients with exophthalmic goiter. Up to December, 1927, tolerance for quinine was studied in 500 patients. Following my preliminary reports, others made similar observations. Among those, Sainton and Schulman [2] arrived at negative conclusions, but their data were based on only ten cases. Pfahler,[3] on the other hand, found the quinine test extremely useful.

THE QUININE TEST AND RESULTS OF USE OF THIS DRUG

The technic of the test consists in giving the patient a dozen capsules each containing 10 grains (0.65 Gm.) of quinine hydrobromide or quinine sulphate, with instructions to take a capsule four times a day. When 20 or 30 grains (1.3 or 1.9 Gm.) have been taken by persons in whom the thyroid function is normal or deficient, symptoms of cinchonism develop. A sense of fulness in the head, impaired hearing with tinnitus, occasional dizziness and headache and less frequently gastric and bladder discomfort are experienced. If, however, the person is suffering with exophthalmic goiter,[4] the daily administration of 30 grains of quinine may be continued with impunity for months, and often distinct improvement is seen in the clinical picture.

The advantages of the quinine test in exophthalmic goiter are its simplicity, its harmlessness and its dependability. The frequency of error is 4.4 per cent in the experiences derived from this series.

Unusual Tolerance to Quinine.—In the 95.6 per cent of patients in whom the quinine test was positive, there was unusual tolerance to the

1. Bram, I.: Quinine Test, M. Rec. **98**:887, 1920; Quinine Test, Second Report, New York M. J. **118**:339, 1923.

2. Sainton, P., and Schulman, E.: Value of Bram Quinine Test in the Diagnosis of Exophthalmic Goiter (Sur la valeur du test de Bram à la quinine comme moyen de diagnostic du goitre exophthalmique), Bull. et mém. Soc. méd. d. hôp. de Paris **45**:1304, 1921.

3. Pfahler, G. E.: The Treatment of Hyperthyroidism by Radiation, M. Clin. N. Amer. **5**:854, 1921.

4. The quinine test was found useful in the confirmation of hyperthyroidism with adenomatous goiter, but the percentage of error was somewhat greater than it was in cases of exophthalmic goiter.

ingestion of quinine. The table indicates the degree of insusceptibility to cinchonism in the series of patients observed. It will be noted that in some cases doses as high as 30 grains were taken three times a day for weeks, without untoward effects. In at least 60 per cent of these patients in whom the reaction to quinine was positive, material amelioration of symptoms was observed. Men seemed able to take larger doses than women. Within two or three weeks an increase in weight occurred in many patients, a lessening of excitability and tremor, reduction in thyroid swelling and exophthalmos, marked lowering of the heart rate and a considerable reduction in the basal metabolic rate.

Quinine in Treatment.—In many patients the therapeutic effect of quinine seems to resemble the remission-producing results of the administration of iodine, with this clinical difference: Iodine cannot be given for more than two or three weeks without danger of aggravating the

Tolerance for Quinine in 500 Cases of Exophthalmic Goiter

Quinine-Negative:	
Patients intolerant to quinine	6 (1.2%)
Patients tolerating 15 grains (0.9 Gm.) daily	16 (3.2%)
Quinine-Positive:	
Patients tolerating 30 grains (1.9 Gm.) daily	158 (31.6%)
Patients tolerating 40 grains (2.6 Gm.) daily	104 (20.8%)
Patients tolerating 60 grains (3.9 Gm.) daily	94 (18.8%)
Patients tolerating 80 grains (5.2 Gm.) daily	68 (13.6%)
Patients tolerating 90 grains (5.8 Gm.) daily	54 (10.8%)
Total	500

symptoms of exophthalmic goiter. Moreover, iodine always increases the thyroid swelling by increasing the colloid content of the organ. Quinine can be given for months, without harm, to patients in whom the test is positive, and its effect on the thyroid gland is that of marked reduction in size.

It must not be construed, however, that quinine, whatever its virtues, is the main factor in the treatment of patients with exophthalmic goiter. A mere drug cannot be depended on for the cure of this disease. Quinine, however, the basis of the Forchheimer treatment, may be regarded as a valuable constituent in the armamentarium of the experienced internist who has sufficient confidence in himself to treat successfully patients with exophthalmic goiter without resorting to an operation.

Intolerance for Quinine.—In six patients marked idiosyncrasy to quinine was observed. In four, this was heralded by erythematous areas on the skin with subdermal swellings, which soon developed into

definite dermatitis with extreme itching and a moderate rise in temperature. Within a week or ten days, desquamation closely resembling that occurring during convalescence from scarlet fever took place. The readministration of as small a dose as 1 or 2 grains (0.06 or 0.1 Gm.) daily for a day or two resulted in the prompt reappearance of untoward effects.

Relative Intolerance for Quinine as an Index to Recovery.—When the basal metabolic rate has become normal and all the signs and symptoms of the disease have disappeared, the patient formerly capable of taking from 30 to 90 grains (1.9 to 5.8 Gm.) of quinine daily complains of a sense of fulness and roaring in the head, some deafness and at times dizziness. The reduction of the dosage even to 15 grains (0.9 Gm.) a day may still elicit evidences of cinchonism. An occasional patient may appear well and still possess a relative immunity to cinchonism; in such instances, there appears to be susceptibility to relapse, indicating the need for further treatment. When, however, a patient formerly not susceptible to cinchonism almost abruptly begins to complain of tinnitus and allied symptoms, and when this cannot be traced to other causes, studies on the basal metabolism will indicate that recovery is at hand, and that the patient is ready to resume his or her customary activities.

CONCLUSIONS

1. In 95.6 per cent of patients with exophthalmic goiter, a relative immunity to cinchonism exists; large doses of quinine may be taken with impunity and even with benefit.

2. This is the basis of the quinine diagnostic test for exophthalmic goiter, which is submitted as an asset in the differentiation of this disease from such conditions as effort syndrome, early tuberculosis, neurasthenia and other conditions commonly confused with exophthalmic goiter.

3. In the form of the hydrobromide or the sulphate, quinine is a valuable constituent of the therapeutic armamentarium of the internist who treats patients with exophthalmic goiter, and should be given in the average case in much larger doses than has been the custom.

EXPERIMENTAL HYPOTENSION IN RABBITS*

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AND
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The prevalence of lowered blood pressure in chronic infections caused us to feel that some of the micro-organisms present in such infections might have properties which lower the blood pressure. The experiments reported were undertaken with this possibility in mind.

MATERIAL AND METHOD

Rabbits were used exclusively in the experiments. Systolic blood pressures were determined in the central artery of the ear according to the method described by Anderson.[1] With his apparatus, the obliteration of the central artery was observed through a rubber membrane. With our apparatus, the rabbit's ear rested on a rubber diaphragm covering a pressure cup and a glass plate was adjusted over the ear so that it just cleared the surface without exerting pressure. Thus observations were made through glass instead of through a rubber diaphragm. A detailed description of the apparatus is given elsewhere.[2] The mean of a series of five consecutive readings was recorded as the pressure, and with rare exceptions the variation of separate readings was not over a few millimeters of mercury. Care was taken at all times to prevent fright or excitement in the animal, and approximately the same portion of the central artery was used for all readings.

After preliminary observations of the blood pressure, rabbits were inoculated with twenty-four hour dextrose brain broth cultures of the composite bacterial flora from the apex of a tooth, a tonsil or prostatic secretion. Teeth were extracted with precautions to avoid contamination, the apexes snipped into sterile Locke's solution and shaken with sand as described by Haden.[3] Material was squeezed from tonsils with a sterile throat mirror. After thorough cleansing of the parts, prostatic fluid was expressed into a sterile Petri dish. Deep tubes of dextrose brain broth were used for cultures in accordance with Rosenow's technic.[4] Rabbits were usually inoculated in groups: one or more were given intravenously 2.5 cc. of a twenty-four hour culture per kilogram of body weight, while the others were inoculated in each knee joint with 0.5 cc. of the same culture. Two rabbits of the series were inoculated in the medullary cavity of the tibia. The tibia was exposed under urethane anesthesia, a hole drilled

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* From the Department of Preventive Medicine, A. O. Smith Corporation.

1. Anderson, H. C.: Demonstration of an Instrument for Taking Repeated Blood Pressures in Rabbits, with Report of Some Experiments, Proc. Soc. Exper. Biol. & Med. **20**:295 (Feb.) 1923.

2. Squier, Theodore L.: Simple Apparatus for Repeated Blood Pressure Determinations in Rabbits, J. Lab. & Clin. Med. **13**:279 (Dec.) 1927.

3. Haden, Russell L.: Elective Localization in the Eye of Bacteria from Infected Teeth, Arch. Int. Med. **32**:828 (Dec.) 1923.

4. Rosenow, E. C.: Studies on Elective Localization; Focal Infection with Special Reference to Oral Sepsis, J. Dent Research **1**:205 (Sept.) 1919.

through the cortex with a dental drill and a small pledget of cotton, which was saturated with a twenty-four hour culture, inserted into the bone marrow cavity. The opening was then plugged with a sterile wooden plug, and the incision was sutured. It was felt that the inoculations into the knee joint and bone marrow would simulate the conditions present in chronic infections.

TABLE 1.—*Results of Inoculation with Cultures from Persons with Low Blood Pressure* *

Culture	Blood Pressure of Patient	Rabbit	Site of Inoculation	Days Preliminary Observation	Days Observed After Inoculation	Mean Pressure Before Inoculation	Minimum Pressure After Inoculation	Pressure Readings Under 32.9 Mm.	Pressure Readings Under 40.1 Mm.	Pressure Readings After Inoculation
471A	94	34	K. J.	51	9	47.6	10	6	7	7
		35	B. M.	51	11	57.6	14	6	7	8
642A	106	33	I. V.	113	18	57.2	10	6	10	14
		54	I. V.	2	18	62.1	14	6	9	14
		65	K. J.	64	7	56.7	12	4	4	6
12T	104	56	I. V.	1	20	58.0	12	4	8	15
		67	K. J.	97	2*	64.8	53	0	0	1
167T	104	109	I. V.	21	3*	66.5	29	1	1	2
		110	K. J.	21	10*	62.5	11	5	6	8
979A	96	152	K. J.	23	160	64.9	8	17	18	62
		153	K. J.	23	80	63.0	10	25	29	41
		58	I. V.	23	3*	67.8	43	0	0	2
1070A	106	177	K. J.	27	67	68.3	16	8	8	29
		178	K. J.	27	65	61.6	23	5	7	25
		179	I. V.	27	10 *	62.6	40	0	2	4
729T	102	204	I. V.	1	62	67.0	41	0	0	31
		205	K. J.	1	32*	65.0	28	3	7	19
		206	K. J.	1	56*	62.4	10	9	14	28
729A	102	219	K. J.	3	53	62.4	47	0	0	22
		220	K. J.	3	54	64.8	42	0	0	22
		221	I. V.	3	41	65.8	19	4	10	21
729A8	102	210	K. J.	43	52	62.1	49	0	0	22
		211	I. V.	43	54	63.4	51	0	0	21
		212	K. J.	43	52	62.7	43	0	0	22
246A	104	362	K. J.	2	26	62.1	44	0	0	15
		363	I. V.	2	27	57.8	29	2	11	15
		364	K. J.	2	27	57.6	30	0	3	15
1091T	88	227	I. V.	13	28	65.4	55	0	0	14
		228	K. J.	13	28	62.0	45	0	0	14
		229	K. J.	13	28	60.8	43	0	0	14
1042P	102	154	I. V.	22	75	65.0	42	0	0	24
		155	K. J.	58	58	57.8	37	0	1	23
		171	K. J.	22	75	67.5	51	0	0	27
20P	100	207	K. J.	7	55	62.4	39	0	0	23
		208	K. J.	7	54	63.1	48	0	0	23
		209	I. V.	7	52	61.6	52	0	0	24
579T	94	299	K. J.	1	12	65.1	44	0	0	10
		300	I. V.	1	19	56.7	46	0	0	10
		301	K. J.	1	12	60.4	41	0	0	10
129A	94	32	K. J.	65	21	68.1	51	0	0	13
		36	B. M.	65	25	64.5	49	0	0	15
		66	K. J.	18	25	70.1	49	0	0	13
1267A	104	317	I. V.	1	30	58.0	41	0	0	10
		318	K. J.	1	30	55.8	46	0	0	10

* In the tables, the letters A, T, or P following culture number designate tooth apex, tonsil and prostate, respectively. Knee joint, intravenous, and bone marrow inoculations are designated K. J., I. V., and B. M., respectively. All rabbits were killed on the day indicated in the column headed "days observed after inoculation" except those marked with an asterisk; these died.

RESULTS

To be reasonably certain that a drop in blood pressure was of significance, the extent of fluctuation in the blood pressure in untreated, supposedly normal, rabbits was determined. Five hundred and forty-six

determinations of average blood pressure (2,730 separate readings) were made on eighty-two normal rabbits. The mean pressure for the group of eighty-two as determined in the central artery of the ear was 62.5 ± 5.0 mm. of mercury. The standard deviation of the pressure was 7.4 mm., and the coefficient of variation was 11.9 per cent. It is of interest that the latter approximates the coefficient of variation of 8.8 to 11.4 per cent found by Alvarez [5] for human blood pressure. The deviation of individual readings from the mean in no instance exceeded four times the standard deviation, and in only nine instances was it more than three times the standard deviation. Consequently, we

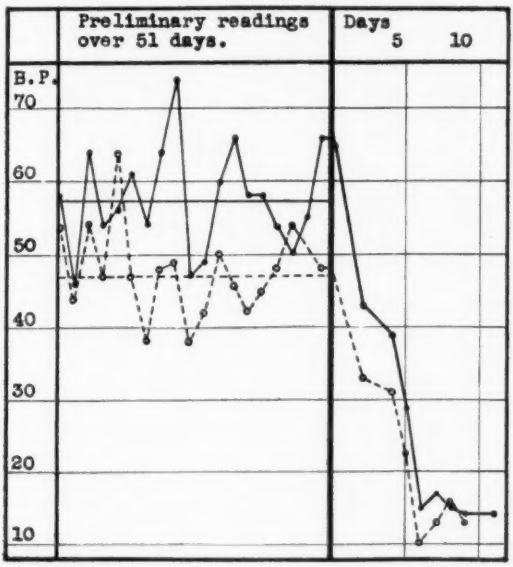

Chart 1.—Blood pressure curves of rabbits inoculated with twenty-four hour dextrose brain broth culture of the apex of a tooth from a person with low blood pressure. The hollow circle and dash line represent the effect on blood pressure of inoculations into the knee joints of rabbit 34, and the black circle and continuous line represent inoculations into the bone marrow of rabbit 33. The heavy vertical line indicates the time of inoculation.

considered a fall in blood pressure to 32.9 mm. (62.5 minus four times the standard deviation 7.4) to be of significance. In the accompanying tables, the number of blood pressure readings falling below 32.9 mm. is recorded for each rabbit and the number falling below 40.1 mm. is

5. Alvarez, Walter C.: Blood Pressure in Fifteen Thousand University Freshmen, Arch. Int. Med. **32**:17 (July) 1923.

also shown. The latter figure represents a fall in blood pressure greater than three times the standard deviation.

Forty-four rabbits were inoculated with sixteen different cultures obtained from persons with a systolic blood pressure under 110 mm. In sixteen of these rabbits (36.8 per cent) the blood pressure subsequently fell to 32.9 mm. or less, while in twenty-three (52.2 per cent) it fell to 40.1 mm. or less. Of the sixteen cultures used, nine produced a significant drop in blood pressure in one or more rabbits (table 1).

A significant drop in blood pressure was observed in all rabbits inoculated with four cultures, and with the other five cultures a signifi-

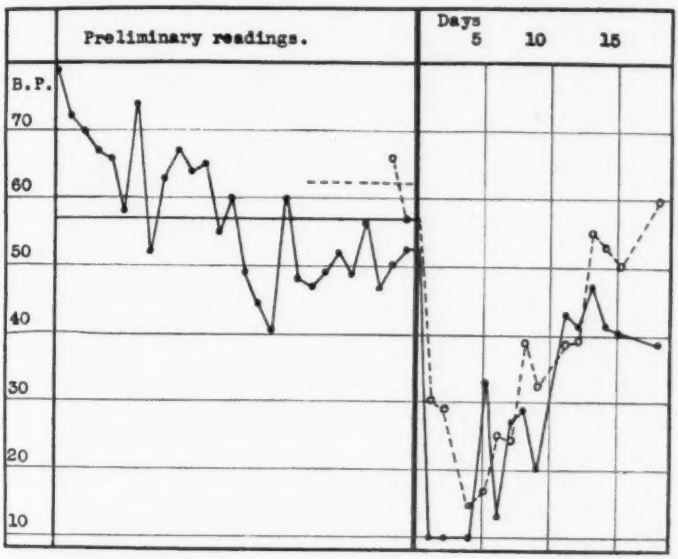

Chart 2.—Blood pressure curves of rabbits inoculated intravenously with twenty-four hour dextrose brain broth culture of the apex of a tooth from a person with low blood pressure. The hollow curve and dash line represent the reaction in rabbit 54, and the black circle and continuous line, the reaction in rabbit 33. The heavy vertical line represents the time of inoculation.

cant drop was observed in one or more of each group. There was a definite tendency toward uniform results in rabbits inoculated in the same manner with a given culture. Each of two rabbits was inoculated in the knee joints with cultures 1203A, 1070A and 729T, and there was a significant drop in all, while, with one exception, rabbits inoculated intravenously with the same cultures did not show any significant fall in blood pressure. One rabbit each inoculated intravenously with cultures 729A and 246A showed a significant lowering of blood pressure,

TABLE 2.—*Results of Inoculation with Bacterial Cultures from Persons with High Blood Pressure*

Culture	Blood Pressure of Patient	Rabbit	Site of Inoculation	Days Preliminary Observation	Days Observed After Inoculation	Mean Pressure Before Inoculation	Minimum Pressure After Inoculation	Pressure Readings Under 32.9 Mm.	Pressure Readings Under 40.1 Mm.	Pressure Readings After Inoculation
1203A	226	313	K. J.	1	36	57.4	28	5	8	12
		314	I. V.	1	31	60.6	35	0		
		315	I. V.	1	31	57.0	32	1	5	12
		316	K. J.	1	31	57.4	22	6	7	11
1168T	242	245	I. V.	1	34	57.6	47	0	0	9
		246	K. J.	1	31	61.4	40	0	1	15
		247	K. J.	1	31	56.0	40	0	6	15
1168A	242	248	I. V.	1	1*	62.2	..	.	.	0
		249	K. J.	1	35	59.6	58	0	0	15
		250	K. J.	1	35	64.2	55	0	0	15

* See footnote table 1.

TABLE 3.—*Results of Inoculation with Bacterial Cultures from Persons with Normal Blood Pressure*

Culture	Blood Pressure of Patient	Rabbit	Site of Inoculation	Days Preliminary Observation	Days Observed After Inoculation	Mean Pressure Before Inoculation	Minimum Pressure After Inoculation	Pressure Readings Under 32.9 Mm.	Pressure Readings Under 40.1 Mm.	Pressure Readings After Inoculation
1214A	130	224	K. J.	6	19	62.7	49	0	0	14
		225	I. V.	6	19	63.2	56	0	0	14
		226	K. J.	6	21	61.0	49	0	0	14
356A	126	271	K. J.	37	40	54.9	44	0	0	9
		272	K. J.	37	40	56.5	50	0	0	14
		273	I. V.	33	40	52.7	48	0	0	14
1274T	98*	206	K. J.	4	12	59.6	38	0	2	11
		207	K. J.	4	13	62.7	47	0	0	11
		208	I. V.	4	13	62.8	47	0	0	11
1952P	124	511	I. V.	..	11	....	60.4	0	0	4
		510	I. V.	..	11	....	62.2	0	0	4
		512	I. V.	..	11	....	57.8	0	0	4
		513	I. V.	..	12	....	57.0	0	0	5
1952T	124	514	I. V.	..	4	....	63.6	0	0	1
		515	I. V.	..	14	....	64.4	0	0	5
		516	I. V.	..	14	....	65.8	0	0	5
93T	124	525	K. J.	1	2	66.4	68.2	0	0	2
		526	I. V.	1	15	68.7	64.8	0	0	7
1263T	122	527	K. J.	1	15	64.8	48.0	0	0	7
		528	I. V.	1	14	73.8	53.4	0	0	7
853A	116	529	K. J.	1	14	65.7	60.0	0	0	7
		530	I. V.	1	14	67.9	64.4	0	0	7
1452T	128	531	K. J.	1	10*	63.5	54.0	0	0	5
		532	I. V.	1	14	69.0	49.0	0	0	7
29T	126	535	I. V.	1	14	61.8	51.8	0	0	7
		536	K. J.	1	15	59.8	59.4	0	0	7
395T	120	534	I. V.	1	15	53.4	54.6	0	0	7
		533	K. J.	1	14	66.6	60.6	0	0	7
1873A	118	537	I. V.	1	13	64.4	55.2	0	0	6
		538	K. J.	1	13	63.6	60.2	0	0	6
1319T	118	539	I. V.	1	13	63.4	59.4	0	0	6
		540	K. J.	1	13	66.2	58.8	0	0	6

* Boy aged 10.

while a change in pressure did not occur in the rabbits inoculated in the knee joints with the same cultures.

The blood pressure curves shown in charts 1 and 2 are typical examples of the reaction observed. The results are shown when one rabbit was inoculated in the knee joints and the other in the bone marrow cavity of the tibia (chart 1). Chart 2 shows the pressure when both rabbits were inoculated intravenously. The blood pressure in most rabbits inoculated intravenously fell rapidly and usually reached a low level about the fourth day after inoculation, after which it gradually rose until about the normal level was reached. In rabbits inoculated in the knee joints or in the bone marrow, the fall in pressure occurred more slowly, and the minimum level was not reached before the sixth day, after which the pressure remained low or rose slowly. The behavior of the blood pressure of rabbits 152 and 153, both inoculated in the knee joints with the same culture, was atypical. In neither rabbit was there a significant drop in pressure until the seventeenth day after

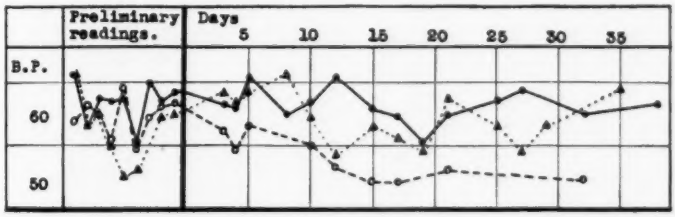

Chart 3.—Blood pressure curves of rabbits inoculated with twenty-four hour dextrose brain broth culture of the apex of a tooth from a person with normal blood pressure. The black circle and solid line represent the curve of the rabbit inoculated intraveneously (R 273); the triangle and dash line represent the blood pressure of rabbit 272; and the hollow circle and dash line, that of rabbit 271, after inoculation into the knee joints. The heavy vertical line indicates the time of inoculation.

inoculation, when it fell from 62 and 63 millimeters to 20 and 32 millimeters, respectively. The pressure remained low in both for about ten days and then rose by roughly half the drop only to fall a few days later to a still lower level, where it remained in both cases until the fifty-eighth day. At this time, a sharp rise in pressure was seen in rabbit 152 followed by another fall and then a rather rapid rise to the normal level, where the blood pressure remained until the rabbit was killed 163 days after the inoculation. On the fifty-eighth day, a slight rise in pressure was also seen in rabbit 153, followed by a fall; then there was another slight rise followed by a fall, which persisted until the animal was killed on the eightieth day after the inoculation. We feel that it is at least plausible to consider that at the periods when the

infecting organisms were active the pressure fell, and as resistance became better and the bacterial activity diminished, the pressure again approached the normal level.

Ten rabbits were inoculated with three different cultures obtained from two persons with a systolic blood pressure of over 220 mm. In three of these rabbits (30.0 per cent), there was a significant fall in pressure (table 2).

Thirty-two rabbits were inoculated with thirteen different cultures obtained from twelve persons with normal blood pressures. Significant changes in blood pressure were not noted in any rabbits of this group (table 3). The blood pressure curves of three rabbits inoculated with one of these cultures are shown in chart 3.

COMMENT

We believe that these experiments demonstrate that certain bacterial cultures can produce a marked fall in the blood pressure of rabbits. In the experiments described, if a fall in blood pressure occurred in one of a group of animals inoculated with a given culture, a fall was usually observed in all animals inoculated in the same manner. Intravenous inoculations produced a drop in blood pressure which reached a minimum level on about the fourth day, after which, as a rule, the pressure gradually returned to normal. When inoculations were made into knee joints or bone marrow, the fall in blood pressure occurred more slowly, but the pressure remained low for a longer time. It has been our experience that an overwhelming infection is not of itself sufficient to cause a significant fall in blood pressure. We have found the blood pressure of rabbits that had been injected intravenously with enormous doses of streptococci to be between 50 and 60 mm. at a time when they were so near death that they were unable to stand.

TABLE 4.—*Summary of Results of Inoculation with Bacterial Cultures*

Blood Pressure of Patients	Cases	Cultures	Cultures Producing Fall in Pressure	Rabbits Inoculated	Rabbits with Pressure Under 32.9 Mm.	Rabbits with Pressure Under 40.1 Mm.
Low	14	16	9	44	16	23
High	2	3	1	10	3	6
Normal	12	13	0	32	0	1

It is possible that certain strains of organisms are able to elaborate in vivo a chemical substance responsible for the marked fall in blood pressure which was seen. Koessler, Lewis and Walker[6] have demonstrated that certain organisms grown in a blood-broth-glycerol-amino-

6. Koessler, Karl K.; Lewis, Julian H., and Walker, Jenny A.: Pharmacodynamic Actions of Bacterial Poison, Arch. Int. Med. **39**:188 (Feb.) 1927.

acid medium form substances which cause arterial constriction in vitro and bronchial constriction in the living pithed guinea-pig. They have found that some of these substances behave like histamine and cause constriction of the arteries in vitro and fall in blood pressure in vivo. Further experiments are being carried on in an effort to demonstrate such a substance in cultures the inoculation of which has been followed by a fall in the blood pressure of rabbits.

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THE UTILIZATION OF JERUSALEM ARTICHOKES BY A PATIENT WITH DIABETES*

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The value of Jerusalem artichokes in the dietetic treatment of persons with diabetes mellitus depends on whether the absence of glycosuria is due to actual absorption and utilization of the carbohydrates or to escape from absorption. A patient of one of us has used large quantities of the dried Jerusalem artichoke in his diet for a number of years, and he volunteered to spend his spring academic vacation of 1926 at the New England Deaconess Hospital, subject to a controlled diet and to various physiologic and chemical observations designed to study this question.

The previous literature with respect to the chemistry and metabolic effect of Jerusalem artichokes and inulin has been reviewed in a recent publication by Root and Baker.[1] They gave baked artichokes containing from 31 to 81 Gm. of carbohydrate in six cases and determined the respiratory exchange by the gasometer method, finding a rise in respiratory quotients from the first to the sixth hour after ingestion, with an upward tendency with respect to duration. In six diabetic cases, the blood sugar was determined before and after the ingestion of artichokes containing from 37 to 81 Gm. of carbohydrate. A slight rise was observed in all cases, with a fall at the end of six hours to values slightly lower than those found before ingestion. These authors drew the conclusion from the respiratory quotients and the blood sugar that the absorption of some reducing sugar due to the taking of artichokes was proved.

OBJECTS AND METHODS OF THE INVESTIGATION

Our object in this investigation was to determine the effects on the course of the respiratory quotient and the gaseous exchange during the day in comparison with the basal metabolism for the day, determined before the first meal, as brought about by the use of a diet in which Jerusalem artichokes furnished the major portion of the carbohydrates. An attempt was also made to determine the amounts of protein, fat and carbohydrate absorbed, as shown by the balance between the intake in the

* From the Nutrition Laboratory of the Carnegie Institution of Washington and the New England Deaconess Hospital, service of Dr. E. P. Joslin.

1. Root, H. F., and Baker, M. L.: Inulin and Artichokes in the Treatment of Diabetes, Arch. Int. Med. **36**:126 (July) 1925.

food and the outgo in the feces, i.e., the so-called digestion coefficients. Supplementary studies of the blood and urine were also made. From the measurements of the respiratory exchange and the nitrogen in the urine, estimates were made of the amounts of the three foodstuffs catabolized in comparison with the amounts calculated as absorbed from the food ingested. Potato, furnishing an equivalent amount of carbohydrate, was then substituted for the artichokes to see what changes in metabolism would take place, and whether the patient could tolerate the carbohydrate in this form.

The respiratory exchange was determined by the gasometer method, a half face mask being used as a breathing appliance and two gasometers connected in such a way that a continuous series of periods of observation could be made. The patient was thoroughly acquainted with the procedure by previous tests. The analyses of air were made by the Haldane portable apparatus and usually by two workers independently, with outdoor air controls, each day before the analyses were begun. Standard methods for the determination of blood sugar, blood carbon dioxide, cholesterol and fatty acids, urinary nitrogen and urinary sugar were used. The food eaten by the patient was duplicated on several days as a composite sample preserved by a substantial addition of xylene, dried and subsequently analyzed. The intention was to obtain a separation of the feces, carmine being used as a marker, but the character and color of the feces were such that the carmine was undetectable, and a separation could not be made. All of the feces voided during the time of the investigation (six days) were collected, preserved with xylene, dried and analyzed. After the samples of foods and feces were partially dried in an oven below 100 C., the remaining moisture was determined by desiccation in a high vacuum at room temperature. The protein was estimated by multiplying the nitrogen by 6.25. A determination of the ether soluble extract was made, and portions of the original dried samples were burned at low red heat in order to estimate the ash. Then the nitrogen-free extract (total carbohydrates) was calculated by adding the protein, moisture, ash and fat and by estimating the balance as total carbohydrates. The reducing sugars and hydrolyzable sugars were extracted and hydrolyzed according to the methods of the Official Agricultural Chemists.[2] The reducing sugars before and after hydrolysis were determined in the extracts by the method of S. R. Benedict.[3] The heats of combustion of the food composites and the feces were determined with the oxycalorimeter of Benedict and Fox.[4]

2. Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, Washington, D. C., 1920, pp. 74 and 95.

3. Benedict, S. R.: A Method for the Estimation of Reducing Sugars, J. Biol. Chem. **9**:57, 1911.

4. Benedict, F. G., and Fox, E. L.: A Method for the Determination of the Energy Value of Foods and Excreta, J. Biol. Chem. **66**:783, 1925.

REPORT OF CASE

History.—The patient, a college professor, developed diabetes at the age of 41 years and 5 months. At the time of the observations here reported, he was 52 years and 8 months old. There was no other case of diabetes in his family. His own past history was unimportant, except for the occurrence of typhoid fever in 1884, 1887 and 1907, and pneumonia. His maximum weight had been 70 Kg. in 1888, and in 1915 he weighed 66 Kg. He came under the treatment of Dr. E. P. Joslin on May 5, 1919. His diet and progress since that time are shown in table 1. He was discharged from the hospital in May, 1919, returned on June 19, 1921, and on Sept. 24, 1922, at which time he began taking insulin. He began using Jerusalem artichokes on Sept. 29, 1923. From that time on, he continued to use the artichokes which he learned to dry in order to have a supply all the year. For several months prior to April, 1926, he had been taking the equivalent of nearly a kilogram of fresh artichokes in a dried form per day. He had found by numerous experiments at home that whereas he could take carbohydrate in that form without causing the appearance of sugar in the urine, he could not add carbohydrate in any other form to his regular diet without causing glycosuria.

TABLE 1.—*Diet, Body Weight and Condition of Patient no. 1500*

	Diet							
Date	Protein, Gm.	Fat, Gm.	Carbohydrates, Gm.	Calories	Body Weight, Kg.	Urinary Sugar	Blood Sugar, per Cent	Insulin Units
May, 1919	60	83	46	1,207	53.5	.....	....	..
June 9, 1919	74	136	50	1,702	....	.....	....	..
June 19, 1921	64	97	29	1,245	....	Not sugar free	0.21	..
Sept. 24, 1922	52	113	26	1,329	44.5	Sugar free	0.23*	2
Feb. 12, 1924	50	110	63	1,442	55	Sugar free	0.10	24
April 3, 1926	46	63	129	1,267	57.5	.....	....	26

* Sept. 28, 1922.

Diet and Food Intake.—The foods eaten daily during the patient's stay of six days in the hospital consisted of the following: from 2 to 4 eggs; 60 Gm. of chicken meat; from 630 to 750 Gm. of 5 per cent vegetables; from 8 to 12 Gm. of butter; 180 Gm. of 20 per cent cream; from 74 to 120 Gm. of washed bran; from 60 to 135 Gm. of mineral oil mayonnaise and 750 Gm. of Irish moss jelly.[5] On every day but April 7 he used 198 Gm. of dried Jerusalem artichokes, and on April 7 he had 500 Gm. of baked potatoes. The bran was thoroughly washed by the patient to remove starch, made into cakes and dried. The dried artichokes were also prepared by the patient and were brought by him to the hospital. The total hydrolyzable carbohydrates of the dried artichokes was about 50 per cent. A sample of the material sent to us by the patient later gave 2 per cent of reducing sugars and 55 per cent of hydrolyzable sugars, and the heat of combustion was 3.4 calories per gram. The hydrolyzable sugar was alcohol-soluble, apparently present in the form of polymers of levulose and not as inulin.

Food composites were collected on four days, and the amount of protein, carbohydrate and fat (including mineral oil) are shown in table 2, as determined by analysis and calculation. The energy derived from each nutrient is calcu-

5. A subsequent analysis of a composite exclusive of bran, mayonnaise and Irish moss jelly gave protein, 46 Gm.; fat, 60 Gm., and carbohydrate, 31 Gm.

lated, and the sum of the calculated calories is compared with the value calculated from the determination by the oxycalorimeter. The computation of the percentages of energy due to each of the three nutrients would result in values too low for protein and carbohydrate and too high for fat, because the total energy is raised by the inclusion of the mineral oil in the composite samples. The presence of mineral oil also complicated the calculation of the energy furnished by fat. The usual value per gram of fat cannot be assigned, as the heat of combustion of mineral oil is higher than fat. There was so much oil in the composite samples that it prevented the drying of the samples, and it was necessary to skim the oil from the surface. Three such samples were obtained, and the heat of combustion was determined by the oxycalorimeter with values of 11.51, 10.64 and 10.35 calories per gram. The average of these three has been used in calculating the energy in the column showing the values for fat. As a check on

TABLE 2.—*Weights of Nutrients, and Distribution of Energy in Food Composites and Feces*

Date, 1926	Weights of Nutrients			Division of Carbohydrates			Distribution of Energy				
	Protein, Gm.	Ether Soluble Extract, Gm.	Nitrogen-Free Extract, Gm.	Reducing Sugars,* Gm.	Hydrolyzable Sugars,* Gm.	Balance, Gm.	Protein, Calories	Ether Soluble Extract, Calories	Nitrogen-Free Extract, Calories	Total Energy Calculated from Sum of Nutrients, Calories	Total Energy Determined by Oxycalorimeter, Calories
Food Composites											
April 3	83	141	285	7	131	147	408	1,525	1,138	3,131	3,199
April 4	75	176	264	43	53	168	422	2,056	1,058	3,536	3,528
April 5	82	130	279	9	113	157	466	1,307	1,117	2,980	3,009
April 7	65	118	259	8†	7†	244	369	1,271	1,037	2,677	2,661
Average per day	76	141	271	17	76	179	431	1,562	1,088	3,081	3,099
Average of 6 days' feces	26	101	66	..	...	66	145	1,159	264	1,502	1,621
Average absorption per day	50	40	205	17	76	113	286	409	824	1,519	1,478

* A sample of the dried artichokes gave 2 per cent of reducing sugars and 55 per cent of hydrolyzable sugars. Therefore, 198 Gm. of dried artichokes must have supplied nearly all of the sugars.

† Artichokes replaced by potato.

the probable accuracy of the calculation of the carbohydrates, the sum of the calories derived from the three nutrients may be compared with that directly determined by the oxycalorimeter. The amounts of carbohydrates in the different days may be taken as probably within 5 per cent of the actual amount present. These carbohydrates include those from bran and the Irish moss as well as those available in the Jerusalem artichokes. The amounts of reducing sugars and total hydrolyzable sugars are also shown in table 2. The total sugars ranged from 93 to 138 Gm., the day on which potatoes were given (April 7) being omitted; on this day they were 15 Gm., which is consistent with the difference in composition of Jerusalem artichokes and of potatoes. The carbohydrates, other than sugars, were more than half of the total carbohydrates and on April 7 were 94 per cent of the total cabohydrates. The agreement between the energy calculated from the sum of the values derived from the weights by analysis and that found by the determination by the oxycalorimeter is satisfactory. The greatest difference was on April 3, i. e., 6.2 per cent and the least on April 4, 0.2 per cent. The average difference was 0.6 per cent.

Composition of Feces and Apparent Absorption of Nutrients.—In table 2 is shown also the average daily excretion of unabsorbed nutrients and oil in the feces. As the diet was essentially constant throughout the six days and similar to that the patient usually had, it is felt that there would not be much error in balancing the amount coming from his food previous to the first day with that which is due to the last day's food and which would be voided after he left the hospital. This patient used sufficient bran and mineral oil in his diet to warrant the belief that the passage of unabsorbed material was not unduly delayed. On the contrary, the investigations of Burrows and Farr,[6] Dutcher, Ely and Honeywell,[7] and Mellanby[8] and Schlaginweit[9] indicated an interference with the absorption of fat in the presence of petroleum oil, and this may account for the fact that although 60 Gm. of fat was supplied in the diet, only 40 Gm. was apparently absorbed. In the calculation of the energy due to fat or oil, the value of 11.47 calories per gram was used, which is the heat of combustion of a mineral oil, because so much of the unabsorbed ether extract must have been due to the mineral oil. The average daily excretion in the feces showed a large amount of ether extract (mineral oil) a smaller amount of carbohydrate and no sugar.

The amounts calculated as absorbed per day give 50 Gm. protein, 40 Gm. ether extract, and 205 Gm. of carbohydrate. Sixty-six per cent of the protein ingested and 76 per cent of the carbohydrates were absorbed, which included all of the sugars and 113 grams of carbohydrates other than sugars. The total energy absorbed was about 1,500 calories. The sugars formed 46 per cent of the total carbohydrates absorbed. If one omits the day on which potato was given, the total sugars ingested were 119 Gm. per day and the other carbohydrates were 157 Gm. per day. The deduction of unabsorbed carbohydrates gives 119 Gm. of sugars and 91 Gm. of other carbohydrates absorbed, so that the sugars formed nearly 57 per cent of the retained carbohydrates, which must have come, in the main, from the Jerusalem artichokes. The distribution of energy in the material retained was protein, 19 per cent; fat, 27 per cent, and carbohydrate, 54 per cent.

The basal metabolism of an average man of 53 years, 57.5 Kg. in weight and 170 cm. tall, according to the Harris and Benedict standard, would be 1,350 calories per day. The apparent available energy was 1,500 calories, so that 11 per cent was available for influence of food and activity. A calculation of the energy production is made later in the paper.

Analyses of Blood.—The results of determinations of sugar, carbon dioxide content, cholesterol and fatty acids in the blood are shown in table 3. The blood sugar gave normal values on the first day in the hospital but on the next two mornings was slightly higher. On the morning of April 7, it was 0.17 per cent in the postabsorptive condition. On this day the patient was given baked potatoes at his first meal at 9 a. m., and at 12:45 p. m. the blood sugar had risen to 0.24; by 7:15 p. m., it was 0.31 per cent, so that the ingestion of potato, which did not contain any more carbohydrate than he had been having in the form of arti-

6. Burrows, M. T., and Farr, W. K.: The Action of Mineral Oil Per Os on the Organism, Proc. Soc. Exper. Biol. & Med. **24**:719 (April) 1927.

7. Dutcher, R. A.; Ely, J. O., and Honeywell, H. E.: Vitamin Studies: XV. Assimilation of Vitamins A and D in Presence of Mineral Oil, Proc. Soc. Exper. Biol. & Med. **24**:953 (June) 1927.

8. Mellanby, J.: Petroleum Emulsion in the Small Intestine, J. Physiol. **64**: XXXIII (Dec.) 1927.

9. Schlaginweit, E.: Untersuchungen über die Darmwirkung des Paraffinum liquidum, Arch. f. exper. Path. u. Pharmakol. **124**:59 (July) 1927.

chokes, caused a marked increase in the blood sugar which continued even until the next morning, when it was 0.27 per cent. However, by 2:45 p. m., on April 8, it was back again at the level of the morning of the 7th. The blood carbon dioxide showed little change in the first two days and was not determined again until three days later, when it was lower. Specific changes did not occur in the cholesterol or fatty acids of the blood during the six days.

Urine.—The urine was collected at frequent intervals during the six days' stay at the hospital; it was tested for diacetic acid and sugar and the total nitrogen determined. After the patient left the hospital, he collected his urine in twenty-four hour periods and sent specimens on for analysis (table 4). The first four days' urine contained an average of 8.3 + Gm. of nitrogen per day equivalent to 0.15 Gm. per kilogram and no sugar or diacetic acid. The calculated protein catabolized is thus about 52 Gm. per day. On the day of the ingestion of potato, there were two marked changes in the urinary elimination. The potato was eaten at 9 a. m., and the first collection of urine after this was

TABLE 3.—*Blood Sugar, Carbon Dioxide Content, Cholesterol and Fatty Acids*

Date, 1926	Time	Sugar, per Cent	Carbon Dioxide, per Cent by Volume	Cholesterol, Mg.	Fatty Acids, Mg.
April 3	P. A.*	0.08	64	308	495
April 3	12:50 p.m.	0.09	64	332	408
April 4	P. A.*	0.14	64	288	...
April 4	9:00 a.m.	....	..	...	398
April 4	9:30 a.m.	0.19	63	280	387
April 4	10:00 a.m.	0.19	61	278	385
April 7	P. A.*	....	..	...	558
April 7	9:40 a.m.	0.17	57	262	...
April 7	12:45 p.m.	0.24	58	262	439
April 7	3:15 p.m.	0.28	57	290	466
April 7	7:15 p.m.	0.31	..	270	...
April 8	P. A.*	0.27	..	308	482
April 8	12:30 p.m.	0.26	..	262	440
April 8	2:45 p.m.	0.16	..	...	...
April 9	P. A.*	0.20	..	...	...

* Postabsorptive, i. e., before breakfast.

at 11:05 a. m., a volume of 93 cc., with 0.3 Gm. of sugar. Collections were again made at 12:39 p. m., 1:29 p. m., 2:47 p. m., 4:22 p. m., 10 p. m., and 7 a. m., on April 8. All of these contained sugar in measurable amounts, the greatest amount occurring in the urine collected at 2:47 p. m., i. e., 2 Gm. The specimens of urine next day showed sugar, including a collection made at 2:48 p. m. After that, sugar was not found on this or succeeding days. After the first meal containing potato, the appearance of sugar in the urine waas prompt, and the specimens continued to show the elimination of sugar for more than twenty-four hours afterward. Simultaneous with the elimination of sugar was a striking increase in elimination of nitrogen on April 7 and 8, and 8 and 9. This cannot be explained as the result of increased protein ingestion on April 7 and 8, as the amount was only 65 Gm. as compared with 75 and 83 Gm. on the other days (table 2). It is difficult to explain this increased elimination of nitrogen. These changes in the urine occurred after the ingestion of potato, which contained as nearly as possible the same amount of carbohydrate as was taken on preceding days in the form of artichokes, and the return to a condition of sugar-free urine, and similar elimination of nitrogen accompanied the resumption of artichokes. No other change was made in the treatment. The patient

received the same amount of insulin at the same intervals as on other days. These changes may be mere coincidence, but it hardly seems likely.

Respiratory Exchange.—In table 5 is given a summary of the measurements of the respiratory exchange as indicated by the oxygen absorption and the respiratory quotient. The general program of measurements was to have four ten-minute periods in succession in a postabsorptive condition after the patient had ridden from the hospital to the laboratory. He then ate his first meal, which contained practically one third of the day's diet. Measurements were then made on him for six successive periods for the duration of an hour, and then after a half-hour's rest a group of six was made. He then ate his noon meal, and again six periods

TABLE 4.—*Statistics of Examinations of Urine*

Date, 1926	Volume, Cc.	Diacetic Acid	Nitrogen, Gm.	Sugar, Gm.
April 3–4	2,160	0	8.1	0
April 4–5	2,680	0	8.3	0
April 5–6	2,270	0	8.0	0
April 6–7	1,700	0	8.9	0
April 7–8	2,427	0	11.8	6.7
April 8–9	2,185	0	10.0	3.8
April 9-10	1,410	0	7.8	0
April 10-11	2,220	0	6.1	0
April 11-12	2,280	0	7.1	0
April 12-13	2,010	..	8.1	..

TABLE 5.—*The Pulse Rate, Oxygen Absorption and Respiratory Quotient of a Diabetic Patient During the Day*

	April 3			April 5			April 6			April 7			April 8		
Time	Pulse	Oxygen, Cc.	Respiratory Quotient	Pulse	Oxygen, Cc.	Respiratory Quotient	Pulse	Oxygen, Cc.	Respiratory Quotient	Pulse	Oxygen, Cc.	Respiratory Quotient	Pulse	Oxygen, Cc.	Respiratory Quotient
Basal 8 – 9 a.m.	55	193	0.85	60	196	0.84	66	193	0.83	60	198	0.84	59	190	0.83
10:00 – 11:00 a.m.	58	218	0.86	63	224	0.85	..	...	....	67	237	0.88	..	...	....
11:30 – 12:30 p.m.	57	209	0.86	60	220	0.85	..	...	....	65	230	0.88	..	...	....
1:30 – 2:45 p.m.	58	220	0.88	63	209	0.88	..	...	....	64	237	0.90	68	234	0.89
3:00 – 4:15 p.m.	56	207	0.91	61	210	0.88	..	...	....	59	225	0.87	64	...	0.88
5:00 – 5:30 p.m.	..	...	....	..	...	....	..	...	....	..	...	....	60	216	0.88
6:40 – 7:30 p.m.	..	...	....	..	...	....	..	...	....	..	...	....	66	225	0.91
8:00 – 9:00 p.m.	..	...	....	..	...	....	..	...	....	..	...	....	59	207	0.90

during the hour were made, followed by a half-hour's rest, and then six more periods were run. This program was carried out on April 3, 5 and 7. On April 6, he felt fatigued, and so measurements were not made other than the four basal periods in the morning. On April 8 the basal periods were made, and the usual morning periods after breakfast were omitted and measurements resumed again after lunch. In addition, between 5 and 5:30 p. m., three more periods were made, and after the evening meal ten more periods were carried out in groups of four and six.

Pulse Rate: The basal pulse, with the exception of April 6, was 60 or under. On April 6, it was somewhat higher. After each meal, the pulse for the first group was always higher than the basal pulse, falling slightly in the second group in the morning and in one case, April 5, back to the basal pulse. In a similar manner after the afternoon meal, the average pulse was higher than the basal but fell again in the later afternoon group.

Oxygen Absorption: The basal oxygen absorption for all five days was within the range of from 190 to 198 cc. per minute. After breakfast the oxygen absorption was increased between 7 and 10 per cent, and the second group in the morning, with the exception of April 7, dropped, but not to the basal figure. The groups in the afternoon gave similar results, with the exception of that of April 5, in which the oxygen absorption was lower than those in the morning but not as low as the basal figure. On April 7, the day on which the patient received potato instead of artichokes, the increase in oxygen absorption, as well as the pulse rate, was more marked than on any other day, although in the first group on the afternoon of April 8, the rise in oxygen absorption was nearly as great as on April 7 at the same time. In the three groups of periods on April 8 during the time in which measurements were not made on the other days, that is, late afternoon and evening, the changes were somewhat similar to those produced by the previous meals on the other days.

Respiratory Quotent: The basal respiratory quotients were narrow in range and were normal. The first meal on each day produced a slight increase, which lasted through both groups of periods in the morning, and the second meal caused the respiratory quotient to rise still higher, so that the highest values occurred in the afternoon. The rise of April 7, the day on which the patient

TABLE 6.—*Estimation of Heat Production from Respiratory Exchange and Urine*

	Calories Produced				Per Cent Distribution		
Date, 1920	Carbohydrate	Fat	Protein	Total	Carbohydrate	Fat	Protein
April 3	728	495	223	1,446	50	34	16
April 5	699	529	221	1,449	48	36	16
April 7	733	495	328	1,557	47	32	21
April 8	691	499	275	1,466	47	34	19

received potato, was more marked in the morning than on the other days. On April 8, the afternoon periods showed about the same increase and the respiratory quotient was raised to a higher point by the evening meal.

In general, then, we have a patient who has a normal basal respiratory quotient, with an increase in pulse rate, oxygen absorption and respiratory quotient, produced by the ingestion of a mixed meal with a large proportion of carbohydrate, about one half of which for four days, was in the form of Jerusalem artichokes.

Heat Production.—The heat production per day was calculated for the four days on which there were periods of determinations of respiratory exchange other than those of the basal metabolism. To obtain a correct estimate of the metabolism for twenty-four hours when there are only intermittent periods of measurement during the day is always difficult. In this series, the basal periods have been used for the time between 10 p. m. and 7 a. m., and the values obtained in the measurements of respiratory exchange during the four days have been apportioned for the rest of the day. To use basal figures for the metabolism during sleep may be questioned, as the metabolism during sleep is undoubtedly depressed. On the other hand, it is probably incorrect to assume that the respiratory quotient had dropped to basal at 10 p. m., so that the average respiratory quotient for the day would probably be higher than that which could be derived from the values in table 5. In addition, allowance was not made for extra muscular activity, although there was some activity other than lying quietly on

the couch in the metabolism experiments. The values for heat production and for energy derived from fat and carbohydrate given in table 6 are therefore minimum values.

For the first two days, the calculated heat productions are almost identical and the last day of the four slightly higher than the first two. On the remaining day, April 7, the heat production was materially higher, and the greatest portion of the increase comes from the protein catabolized. This was the day on which potato was used instead of Jerusalem artichoke. Not only was there a disturbance in the metabolism in that sugar was excreted and protein utilization increased, but the metabolism was raised, and to a slight extent this was carried over to the next day.

The distribution of the energy derived from the three nutrients indicated that about 50 per cent came from carbohydrates, under 35 per cent from fat and from 16 to 21 per cent from protein. There was thus a large proportion from carbohydrate and an adequate proportion from protein. If 10 per cent additional is allowed for extra activity, there would be an increase of about 150 calories a day. If this amount is apportioned to carbohydrate and fat in the ratio of 50:35, there would result an increase of 88 calories in the carbohydrate portion and 62 calories in the fat portion. The percentage due to carbohydrate and fat would be increased, while the percentage due to protein would be decreased. The average energy derived from carbohydrate was 713 calories as a minimum, which would be furnished by 178 Gm., while the addition of 88 calories due to extra activity would increase it 22 Gm., making 200 Gm. as a probable maximum of carbohydrates burned. The food eaten during the period indicated in table 2 contained 271 Gm. on the average, and the amount calculated as absorbed was 205 Gm., so that the diet supplied the patient with an amount of carbohydrate which was about equal to that burned as calculated from the metabolism. It was estimated that about 1,500 calories was furnished by the absorbed food. The minimum energy produced, as calculated in table 6, is under this with the exception of the "potato" day, April 7. If an allowance of 10 per cent is made for extra activity, the energy in the food supplied would be about 100 calories too low.

The main problem in this investigation was whether Jerusalem artichokes supplying a large amount of carbohydrates in the diet of a patient with diabetes were absorbed and utilized in the metabolism. The results indicate that the daily intake of dry nitrogen-free, fat-free substances was 270 Gm., of which 30 Gm. was derived from 5 per cent vegetables and cream, 100 was supplied by artichokes and the remainder consisted of unknown substances from Irish moss and bran; that about 205 Gm. of carbohydrate was absorbed, and that from 175 to 200 Gm. was burned in the body. The results show definitely that Jerusalem artichokes can furnish absorbable carbohydrates which are utilized by a diabetic patient.

SUMMARY

The metabolism of a patient with diabetes mellitus in whose diet Jerusalem artichokes furnished one-half the carbohydrates was studied for six days with reference to the gaseous exchange, absorption of food and composition of blood and urine.

The analyses of composites of the food ingested on four days showed an average intake of 76 Gm. of protein and 271 Gm. of dry nitrogen-free and fat-free substances. On five of the six days, Jerusalem artichokes provided more than 100 Gm. of carbohydrates, supplying about

95 per cent of the hydrolyzable sugar. On one day the artichokes were replaced with baked potatoes containing an equivalent amount of carbohydrates.

The analyses of six days' feces indicated an average daily absorption of protein, 50 Gm.; fat, 40 Gm. and carbohydrates, 205 Gm., with a total energy content of about 1,500 calories.

The average basal respiratory quotient was 0.84. The food intake divided into three equal portions during the day produced a rise of the respiratory quotient to 0.91 and a maximum increase in the oxygen consumption of 14 per cent.

Although this patient had been sugar free for some time on a diet in which artichokes furnished the greater portion of the carbohydrates, the substitution of an equivalent amount of carbohydrates in baked potatoes on one day was accompanied by an increased excretion of urinary nitrogen, the prompt appearance of sugar in the urine, a rise in the blood sugar and an increase in the heat production. The resumption of Jerusalem artichokes on the next day was accompanied by a disappearance of urinary sugar, a lowering of blood sugar and a lowering of the metabolism of energy.

A calculation of heat production on four days gave from 1,450 to 1,550 calories per twenty-four hours (minimum, not maximum, values), with 50 per cent from carbohydrates, from 32 to 36 per cent from fat, and from 16 to 21 per cent from protein.

The results show that Jerusalem artichokes furnish carbohydrates which can be absorbed and utilized by a patient with diabetes mellitus.

DISEASE OF THE CORONARY ARTERIES

ITS OCCURRENCE WITHOUT GROSS CARDIAC HYPERTROPHY *

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Cardiac hypertrophy is frequently found at autopsy in persons with disease of the coronary arteries. An extracoronary mechanism is nearly always responsible for this hypertrophy. In this report, however, we wish to emphasize that gross cardiac hypertrophy is often absent in disease of the coronary arteries even though other marked pathologic changes of the vessels and heart are present.

The term disease of the coronary vessels as employed here needs clarification. It is, of course, well known that the coronary vessels often appear arteriosclerotic at necropsy. But this condition, in a strict sense, is not a disease; it probably represents a metabolic process assailing many structures, among them blood vessels. The arteriosclerotic alteration of such vessels is, in a certain respect, the testimony and stigma of advancing years. Markedly sclerotic vessels are sometimes seen in comparatively young persons; generally, however, arteriosclerosis occurs in the later decades of life and attacks the arterial tree as a whole or else limits itself to one or more circumscribed arterial circuits, i.e., the cerebral, pulmonary or coronary, and involvement of any of these circulatory systems may persist and may be clinically symptomless.

We are, however, interested in disease of the coronary vessels in the sense that some other factor or process, related to or independent of arteriosclerosis, blocks or narrows the vessels, thus producing pathologic alteration of the muscle of the heart. In many instances, the sclerotic walls of the coronary vessels gradually encroach on the lumen of the vessels, eventually causing obliteration. In other cases a superimposed thrombus occludes a vessel that is already the seat of arteriosclerosis. Here the formation of a thrombus may have resulted from the sclerotic process or may be the product of some independent and unknown phenomenon. In many of these circumstances the muscle of the heart may suffer severely and the damage reveal itself by clinical or graphic manifestations. Such hearts damaged by impaired coronary circulation and altered by attendant injury to the muscle may remain grossly unhypertrophied and even small. This does not call for further comment

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here, nor do we now raise the question whether disease of the coronary vessels can of itself produce cardiac hypertrophy. Our interest is chiefly in a series of patients on whom observation at autopsy disclosed unmistakable crippling of the coronary vessels by either occlusion or gradual obliteration, associated with much injury to the muscle of the heart; the clinical legends of these patients often indicated interference in the coronary vessels, and at death their hearts were not grossly hypertrophied.

These patients had marked atherosclerosis with slow narrowing or complete occlusion of the vessels. Patients with syphilitic arteritis, productive endarteritis and periarteritis nodosa were excluded. Cases of recent occlusion were not considered. The sclerotic process in all instances involved both the right and the left branches; the left coronary artery was predominantly involved in nine cases; and in four cases the right coronary artery was principally diseased. The effect of the sclerosis varied from marked stenosis and partial occlusion to complete closure. The orifices were greatly narrowed in two cases, and the mouth of the right coronary artery was entirely closed in one case. The gross myocardial changes ranged from small scattered and large confluent areas of fibrosis to various degrees of multiple infarction; two cases showed parietal aneurysms of the ventricular wall.

All these patients had unhypertrophied hearts and thus illustrate the contention that *indisputable and advanced coronary disease need not lead to gross cardiac hypertrophy.*

This is not a new view, but we feel that it deserves emphasis. However, the literature, in general, does not contain many definite references on this subject. As far back as 1882, Huber [1] stated that hypertrophy of the left ventricle "bears no relation to myocardial and coronary disease." In more recent years, occasionally one comes on a reference to a small unhypertrophied heart found at autopsy in the presence of coronary thrombosis or closure by an obliterating process. Thus, Faulkner, Marble and White [2] observed the heart unhypertrophied in three out of a total of thirty cases in which there was complete or practically complete occlusion. Herrick [3] published three reports of necropsy in patients with coronary thrombosis, in two of whom the hearts were normal in size. Acker [4] described a single similar case. Hamman [5]

1. Huber, K.: Ueber den Einfluss der Kranzarterienerkrankungen auf das Herz und die chronische myocarditis, Virchows Arch. f. path. Anat. **89**:236, 1882.

2. Faulkner, J. M.; Marble, H. C., and White, P. D.: Differential Diagnosis of Coronary Occlusion and of Cholelithiasis, J. A. M. A. **83**:2080 (Dec. 27) 1924.

3. Herrick, J. B.: Thrombosis of the Coronary Arteries, J. A. M. A. **72**:387 (Feb. 8) 1919.

4. Acker, R. B.: Delayed Death in Coronary Thrombosis, J. A. M. A. **73**: 1692 (Nov. 29) 1919.

5. Hamman: Symptoms of Coronary Occlusion, Bull. Johns Hopkins Hosp. **38**:273, 1926.

Observations in Nineteen Cases of Advanced Disease of the Coronary Arteries with Coexisting Marked Myocardial Changes (in Seventeen Cases) but Without Gross Hypertrophy of the Heart

Age, Year	Sex	Weght of Heart, Gm.	Coronary Vessels	Myocardium
43	M	200	Orifices narrowed by intimal thickening and arteries on section show numerous scattered areas of calcification with partial stenosis of lumen	Not described
47	M	270	Descending branch of left coronary vessel shows extensive changes in its wall; intima is ulcerated; small adherent mural thrombi	Grayish fibrous scars with scattered streaking in the muscle
58	M	200	Tortuous with scattered calcified plaques and in some places stenosis	Decidedly browner than average
58	F	320	Marked atheromatous involvement with slight stenosis; right orifice greatly narrowed; entire vessel small	Marked fibrosis left ventricle; near apex, area 2 cm. in diameter in which muscle is replaced by fibrous tissue
61	M	300	Marked diffuse thickening; scattered atherosclerotic plaques in intima with marked stenosis of lumen in places	Fibers coarser than average
61	M	400	Mouth of right coronary vessel completely obstructed; left coronary vessel completely obstructed by calcified atherosclerotic process	Wall of left interventricular septum soft and possibly infarcted and necrotic
65	M	340	In numerous areas, arteries pipestem in character with considerable stenosis of lumen in portions	In left myocardium, large firm pearly gray area replacing muscle
65	M	300	Pipestem with considerable stenosis in places	Architecture of left myocardium coarse
65	M	300	Anterior descending branch of left coronary vessel completely occluded by small atherosclerotic plaques	Old infarct of left ventricle apex
65	F	220	Lumen of right coronary vessel completely obliterated by soft atheroma	Extensive fibrous streaking; several small foci of necrosis near apex
66	M	260	Markedly sclerotic with narrowed lumens	Slight fibrosis about the small vessels
67	F	200	Marked arteriosclerotic involvement and almost complete occlusion of small branch of right coronary vessel	In anterior half of apical region of left ventricle large healed infarct
67	M	340	Marked narrowing by arteriosclerotic plaques with complete occlusion in one area	Moderate dilatation of left ventricle due to marked thinning out of wall in posterior part beginning at interventricular septum and involving half of circumference of left ventricle
68	M	280	Marked atherosclerotic plaques in both vessels; lumen of branch to left ventricle practically obliterated at one point by extensive calcified plaque	Musculature pale reddish brown, a few gray translucent flecks replacing muscle cells
70	F	270	Lumen of left coronary vessel considerably stenosed in places	Slight fibrosis of left myocardium
75	F	300	Moderate atheromatosis with thickening; circumflex branch to left border of heart shows marked calcification with practically complete occlusion	Pale, brown; slight fibrous streaking about small vessels
75	F	350	Marked atherosclerotic involvement with stenosis	Fine linear fibrous streaking
91	F	280	Pipestem with marked stenosis of lumen	Fibers coarse
96	F	300	Marked atherosclerotic thickening with partial occlusion	Not described

stated that the area of cardiac dulness need not be enlarged in persons with coronary occlusion. Nathanson [6] reviewed 113 cases of severe coronary disease with marked narrowing and partial obliteration of one or more large arteries with well defined changes in the heart muscle, and in forty-five cases the heart was not enlarged, weighing 400 Gm. or less. In a paper published this year on cardiac infarction and coronary thrombosis, Parkinson and Bedford [7] made the casual statement that "cardiac enlargement is not a feature," though they were of the opinion that coronary disease alone can cause some degree of hypertrophy. Experimentally, Hamburger, Priest and Bettmann [8] did not observe hypertrophy of the heart six months after the artificial introduction of lycopodium spores into the coronary vessels.

It would lead us too far afield to speculate on the causes for this absence of hypertrophy. We wish to indicate, however, that the occurrence of hypertrophy may bear some relation to the ability of the heart to develop an adequate collateral circulation. This ability is variable, as has been demonstrated by anatomic studies. Thus, Gross [9] found that the heart is abundantly provided with capillary and precapillary anastomoses which are normally not in use and that these are inadequate for emergencies but may become adequate when the coronary obstruction is gradual. More recently Kugel [10] demonstrated a constant interauricular coronary vessel that is possibly capable of enlarging and carrying on the circulatory needs when any of the major branches suffer. Furthermore, Oberhelman and LeCount [11] noted that in hearts with extensive myocardial changes and with incomplete or total occlusion of one or more coronary arteries, abundant collateral circulation was present. The more gradual the occlusion, the more marked was the compensatory anastomoses that developed. Benson and Hunter [12] directed attention to the frequent occurrence of supernumerary coronary orifices in persons with coronary arterial disease, such supernumerary openings conceivably functioning as sources for collateral circulation.

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6. Nathanson, M. H.: Diseases of the Coronary Arteries, Am. J. M. Sc. **170**:240, 1925.

7. Parkinson, John; and Bedford, D. Evan: Cardiac Infarction and Coronary Thrombosis, Lancet **1**:5, 1928.

8. Hamburger, Walter W.; Priest, Walter, S., and Bettmann, Ralph B.: Experimental Coronary Embolism, Am. J. M. Sc. **170**:168, 1926.

9. Gross, L.: The Blood Supply to the Heart in Its Anatomic and Clinical Aspects, New York, Paul B. Hoeber, 1921.

10. Kugel, M. A.: An Important Anastomotic Blood Vessel in the Auricle of the Human Heart, Proc. Path. Soc., Nov. 10, 1927.

11. Oberhelman, H. A., and LeCount, E. R.: Variations in Anastomosis of Coronary Arteries and Their Consequences, J. A. M. A. **82**:1321 (April 26) 1924.

12. Benson, R. L., and Hunter, W. C.: The Pathology of Coronary Arterial Disease, Northwest Med. **24**:606 (Dec.) 1925.

Accordingly, the capacity of a heart to produce and develop collateral circulation in the face of gradual interference with coronary flow may possibly depend on the anatomic arrangement of the coronary vessels—in other words, on a congenital endowment of pattern and of potential development for coronary anastomoses. When adequate collateral circulation is established, one would not expect cardiac hypertrophy as a consequence to disease of the coronary arteries. When seemingly unexplained hypertrophy accompanies disease of the coronary arteries, one would search for an insufficient, undeveloped collateral coronary circulation.

CONCLUSIONS

1. In cases of marked disease of the coronary vessels, together with a diseased heart on gross examination, the heart was found to be unhypertrophied and even small, as revealed at autopsy in the nineteen cases we have tabulated.

2. We had two patients with disease of the coronary arteries in whom clinical manifestations and roentgen-ray evidence pointed to cardiac enlargement. These hearts were dilated; they should not mistakenly be considered hypertrophied.

3. It may be that in the patients with disease of the coronary arteries in whom the heart remained small, the organ failed to hypertrophy because it possessed a potential mechanism ready to function through adequate collateral channels whenever the coronary circulation was gradually blocked or impeded.

ALKALOSIS IN PATIENTS WITH PEPTIC ULCER *

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Although toxic symptoms in certain patients being treated for peptic ulcer were observed by Sippy and his co-workers and some study of the blood chemistry had been carried out in a considerable number of these patients, the results were apparently not considered of sufficient importance to warrant their publication. The first observations concerning the intoxication produced by the administration of large amounts of alkali in the Sippy treatment to be recorded in detail were those of Hardt and Rivers [1] in 1923. They pointed out that "patients with duodenal ulcer treated by the Sippy method may develop definite symptoms of toxemia associated with renal changes, increased blood urea, and normal or increased carbon dioxide combining power of the plasma"; they asserted also that "patients with duodenal ulcer and renal complications are more inclined to develop these toxic manifestations and to a much greater degree." Shortly after the report of Hardt and Rivers, another paper appeared from the Mayo Clinic by Brown, Eustermann, Hartman and Rowntree,[2] in which the authors carefully discussed the toxemia occurring in pyloric and in duodenal obstruction. A detailed study of eleven cases was presented in which, as the result of organic obstruction or of anatomic or physiologic stasis in the duodenum, duodenal toxemia developed. They stated: "Duodenal toxemia is characterized by a clinical syndrome, by urinary changes, by pathognomonic changes in the chemistry of the blood, by decreased renal function, and in case of death by pathologic changes in the kidney." The increased carbon dioxide combining power of the plasma with low plasma chloride was regarded as indicating the existence of this

* From the Departments of Internal Medicine and Biochemistry, The State University of Iowa, Iowa City.

1. Hardt, L. L., and Rivers, A. B.: Toxic Manifestations Following the Treatment of Peptic Ulcer, Arch. Int. Med. **31**:171 (Feb.) 1923.

2. Brown, G. E.; Eustermann, G. B.; Hartman, H. R., and Rowntree, L. G.: Toxic Nephritis in Pyloric and Duodenal Obstruction. Renal Insufficiency Complicating Gastric Tetany, Arch. Int. Med. **32**:425 (Sept.) 1923.

toxemia, and when this was associated with evidence of renal insufficiency, increased blood urea, etc., the diagnosis was considered definite. These authors regarded the degree of chemical disturbance as reflected evidence of the extent of the damage.

When one compares the symptomatology of duodenal toxemia resulting from obstruction with the toxemia encountered in the alkali treatment of persons with peptic ulcer, one is struck by their similarity and is inclined to wonder if possibly the alkalosis is not quite as important an etiologic factor in the toxemia of duodenal obstruction as the supposed specific toxin absorbed from the gastro-intestinal tract.

Previous to the publication of Hardt and Rivers' [1] paper, toxic manifestations following the administration of sodium bicarbonate had been reported by several investigators, notably Howland and Marriott,[3] Harrop [4] and Grant.[5] One of Grant's patients was undergoing Sippy treatment for peptic ulcer. This patient developed symptoms of alkalosis and tetany and had a carbon dioxide combining power of 91 per cent by volume.

Shortly after the publication of the paper by Hardt and Rivers, papers appeared by Kantor [6] and by Shattuck, Rohdenburg and Booher [7] in which an effort was made to neutralize the hydrochloric acid by other antacids than sodium bicarbonate. Following the suggestion of Greenwald,[8] tertiary phosphates of magnesium and calcium were employed. Symptoms of alkalosis were not observed, although these gastric antacids were shown to act efficiently in neutralizing the hydrochloric acid. In the six cases carefully studied by Shattuck, Rohdenburg and Booher, the p_H and carbon dioxide remained essentially normal. Two patients with peptic ulcer who developed typical symptoms of alkalosis under Sippy management are described by Shattuck.

It is of interest that several years earlier a considerable number of estimations of carbon dioxide were made by one of us (M) on patients of Dr. Shattuck under Sippy management. At that time we did not encounter a single patient in whom the carbon dioxide was

3. Howland, John; and Marriott, W. M.: Observations upon the Calcium Content of the Blood in Infantile Tetany and upon the Effect of Treatment by Calcium, Quart. J. Med. **11**:289 (July) 1918.

4. Harrop, G. A.: The Production of Tetany by the Intravenous Infusion of Sodium Bicarbonate, Bull. Johns Hopkins Hosp. **30**:62 (March) 1919.

5. Grant, S. B.: Tetany. A Report of Cases with Acid-Base Disturbance, Arch. Int. Med. **30**:355 (Sept.) 1922.

6. Kantor, J. L.: Antacid Gastric Therapy, with Special Reference to the Use of Neutral Antacids, J. A. M. A. **81**:816 (Sept. 8) 1923.

7. Shattuck, H. F.; Rohdenburg, E. L., and Booher, L. E.: Antacids in the Medical Management of Peptic Ulcer, J. A. M. A. **82**:200 (Jan. 19) 1924.

8. Greenwald, I.: Gastric Antacids which Cannot Act as Systemic Alkalis, Proc. Soc. Exper. Biol. & Med. **20**:436 (May) 1923.

notably high, possibly for the reason that all bloods were taken in the morning (table 3), although this was the particular object of those determinations. We were then aware that many persons with ulcer showed evidence of impaired renal function.[9]

The earlier reports on alkalosis did not include the estimation of the blood p_H, although the carbon dioxide combining power was found high when estimated. Binger, Hastings and Neil[10] were apparently the first to determine the blood p_H in a case of alkalosis due to the administration of sodium bicarbonate. They found a p_H of 7.55, thus proving the presence of an uncompensated alkalosis. A year later Kast, Myers and Schmitz[11] reported observations on twenty patients with alkalosis, in ten of whom the alkalosis was due to the administration of sodium bicarbonate. Determinations of the blood p_H were made in all cases, the highest figure being 7.6. Four of the patients had peptic ulcers and were undergoing Sippy treatment.

Ellis[12] presented a discussion of four cases of alkalemia, two being due to overdosing with sodium bicarbonate. He stated:

> The symptoms of poisoning with sodium bicarbonate as given by Hardt and Rivers are in agreement with those noted in these cases. The patients are unduly introspective and nervous. They are irritable and complain of trifles. There is headache, nausea and vomiting, dizziness, vertigo and lightheadedness. They complain of aching pains in the muscles and joints. There is weakness followed by absolute prostration. They become apathetic, drowsy and are aroused with difficulty, and finally tetany and convulsions supervene.

McVicar,[13] following the work of Brown, Eustermann, Hartman and Rowntree at the Mayo Clinic, reported a study of thirty cases of obstruction in the upper gastro-intestinal tract, and emphasized the value of a characteristic blood chemistry, namely, the rise in the blood urea and carbon dioxide and the fall in the plasma chloride, in the diagnosis, prognosis and treatment. He pointed out that tetany may be anticipated when the carbon dioxide combining power of the plasma is found to be above 100 per cent by volume.

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9. Myers, V. C.: Chemical Changes in the Blood in Disease: I. Nonprotein and Urea Nitrogen, J. Lab. & Clin. Med. **5**:420 (April) 1920.

10. Binger, C. A. L., Hastings, A. B., and Neil, J. M.: Edema Associated with Moderate Bicarbonate Administration During Convalescence from Pneumonia, Arch. Int. Med. **32**:145 (Jan.) 1923.

11. Kast, L.; Myers, V. C., and Schmitz, H. W.: Clinical Conditions of Alkalosis, J. A. M. A. **82**:1858 (June 7) 1924.

12. Ellis, A. W. M.: Disturbance of the Acid-Base Equilibrium of the Blood to the Alkaline Side: Alkalaemia, Quart. J. Med. **17**:405 (July) 1924.

13. McVicar, C. S.: A Discussion of the Clinical and Laboratory Findings in Certain Cases of Obstruction in the Upper Gastro-Intestinal Tract. The Rôle of Blood Chemistry in Diagnosis, Prognosis and Treatment of this Condition, Am. J. M. Sc. **169**:224, 1925.

Extraordinary "nervous and mental symptoms due to alkalemia and renal insufficiency, following obstruction in the region of the pylorus and the alkaline treatment of duodenal ulcer" have been reported by Houghton and Venables.[14] Uremic symptoms with epileptiform convulsions in pyloric obstruction in patients in whom alkalis were not used were attributed by Houghton to loss of hydrochloric acid in the vomitus and a toxic degenerative nephritis with retention of nitrogen. These authors apparently emphasized the nitrogen retention in the blood rather than the alkalemia. Their laboratory data include only figures for the blood urea which was elevated in all cases. The toxic nephritis has been attributed by various authors to a specific toxin entering the circulation from the wall of the obstructed duodenum. The increase in the urea and nonprotein nitrogen in the blood, however, has been observed in patients both with and without any obstruction in whom marked alkalosis was present. There was obstruction in only one of the seven cases reported by Venables. It seems likely that at least a part of the increase in the nonprotein nitrogen is due to a systemic change with excessive protein destruction rather than the result of renal retention, though in the most severe forms of alkalosis a well defined nephritis occurs as a part of the intoxication.

Last year Jordan[15] reported observations on the carbon dioxide, chloride and calcium content of the blood of forty-one patients with peptic ulcer under Sippy treatment. She concluded:

> It is suggested by the estimations made that the acid-base equilibrium is at first somewhat disturbed by the influx of alkalis, but, within a few days, levels of chloride and carbon dioxide content which approach normal are reached, and in the large majority of cases there is no chemical or clinical disturbance due to alkalosis. In the small percentage of cases that show clinical signs of alkalemia the carbon dioxide content shows a marked rise, the calcium content tends to rise, and the plasma chloride to diminish. The level of carbon dioxide content at which symptoms appeared in these cases is 70 per cent by volume.

Koehler[16] recently reported some interesting observations on four patients with lead poisoning who were alkalinized for a considerable

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14. Hurst, A. F.; Houghton, L. W., Venables, J. F., and Lloyd, N. L.: Nervous Symptoms Due to Alkalaemia and Renal Insufficiency Following Obstruction in the Region of the Pylorus and the Alkaline Treatment of Duodenal Ulcer. Introduction (Lloyd). A. Three Cases of Toxemia Following Obstruction Near the Pylorus (Houghton). B. Seven Cases of Alkalosis Following Alkaline Treatment of Duodenal Ulcer (Venables). C. Two Cases of Pyloric Obstruction with Alkalemia and Renal Insufficiency but No Nervous Symptoms (Lloyd), Guy's Hosp. Rep. **75**:147, 149, 152, 157 (April) 1925.

15. Jordan, S. M.: Calcium, Chloride and Carbon Dioxide Content of Venous Blood in Cases of Gastroduodenal Ulcer Treated with Alkalis, J. A. M. A. **87**: 1905 (Dec. 4) 1926.

16. Koehler, A. E.: The Effect of Acid and Base Ingestion upon the Acid-Base Balance, J. Biol. Chem. **72**:99 (March) 1927.

period. Forty grams of sodium bicarbonate or an equivalent amount of sodium citrate were used daily. With this therapy, a blood p_H of 7.50 to 7.55 could be maintained for several weeks. The accompanying carbon dioxide content varied between 65 and 70 per cent by volume. The amount of sodium bicarbonate used in the routine Sippy treatment, that is, in the average case, is a little less than that used by Koehler in the treatment of persons with lead poisoning but the total amount of alkali used in the treatment of persons with ulcer is at least from 10 to 20 per cent greater. That the symptoms of acidosis and alkalosis may be similar was pointed out by Myers and Booher,[17] and Koehler [16] strongly emphasized this point. He stated: "In our study practically every symptom elicited during acidosis was noted during alkalosis, namely, loss of appetite, lassitude, listlessness, headache, nausea and drowsiness."

PRESENT STUDY

This study was primarily undertaken to determine the effect on the blood chemistry produced by the alkalis administered in the treatment of persons with peptic ulcer. Other incidental problems came up in the course of the study. We were interested in finding out how frequently the clinical symptoms of alkalosis accompanied definite changes in the acid-base equilibrium. We also made some study of the effect of the various alkalis used in the routine treatment, the effect of vomiting and aspiration of large quantities of gastric juice and the shift of the acid-base balance after relief of pyloric obstruction by gastro-enterostomy. Consideration was also given to the blood chemistry in conditions other than ulcer of the stomach and duodenum. In spite of the fact that there are only a few of these cases, they are of interest in this connection because of one or more symptoms in common with certain forms of peptic ulcer. Some of these results are included at the end of the general table (table 1).

The patients used for this study were chiefly persons from the medical wards who were receiving treatment for peptic ulcer. In general, when surgical treatment offered more than medical treatment, operations have been advised or urged. Obstruction at the pylorus has been an indication for surgical treatment as a rule, but when operation was refused these patients with obstruction were necessarily treated medically and some of them, especially when they suffered from pain, received alkalis. In our treatment of patients with peptic ulcer we have attempted to individualize as much as possible.[18]

17. Myers, V. C., and Booher, L. E.: Some Variations in the Acid-Base Balance of the Blood in Disease, J. Biol. Chem. **59**:699 (April) 1924.

18. Gatewood, W. E.: Cooperation in the Management of Peptic Ulcer, J. Iowa State M. Soc. **16**:23 (May) 1926.

TABLE 1.—*Data on Acid-Base Balance of Blood in Patients with Peptic Ulcer Receiving Alkalis, Including Observations on Several Miscellaneous Conditions*

Case	Age	Sex	Date, 1926-1927	Electrometric *pH*	Plasma Carbon Dioxide Content, Cc.	Plasma Chlorine as Sodium Chloride, Mg.	Serum Sodium, Mg.	Hemoglobin, Gm.	Nonprotein Nitrogen, Mg.	Urea Nitrogen, Mg.	Diagnosis; Comment
1. G. L.	53	M	Jan. 5, a.m.	7.6+*	120.0	...	...	....	....	....	Duodenal ulcer with obstruction. No alkalis; marked symptoms of alkalosis; gastro-enterostomy, Jan. 12, 1927; markedly improved before operation by intravenous injection of 10 per cent dextrose in isotonic salt solution
			Jan. 24, a.m.	7.37	71.1	550	...	11.7	....	22.8	
			Feb. 23, p.m.	7.43*	57.0						
2. C. D.	66	M	Nov. 1, a.m.	7.48	77.8	606	...	10.9	....	18.1	Duodenal ulcer. Mild symptoms after routine alkalis for eight days
			Nov. 8, a.m.	7.55	78.7	572	...	9.7	....	18.2	
			Nov. 13, a.m.	....	75.8	594	...	6.1	....	19.1	
3. R. P.	33	M	Dec. 10, a.m.	7.38	57.9	575	323	17.3	30.8	....	Duodenal ulcer, December 10, before alkalis. December 13, after routine alkalis for three days, nervousness, headache, muscle-ache, anorexia, vomiting; February 11, on routine alkalis, marked symptoms; February 22, on calcined magnesia and calcium carbonate, no symptoms
			Dec. 12, a.m.	7.48*	68.8	575	350	14.5			
			Dec. 13, a.m.	7.54	81.5	574	326	16.3	31.2	13.9	
			Feb. 11, p.m.	7.56*	74.9	563	332				
			Feb. 12, a.m.	7.41	50.4	594	326	13.8	28.0		
			Feb. 22, p.m.	7.45*	56.0						
			Feb. 23, a.m.	7.33*	56.0						
			Mar. 18, p.m.	7.50*	57.9	550	326	13.6	32.4		
			Mar. 19, a.m.	7.39*	53.2	569	350	13.6	30.0		
4. D. B.	48	F	Feb. 18, a.m.	7.40	49.4	...	...	....	....	....	Duodenal ulcer with slight obstruction. February 18, before alkalis. February 25, after routine alkalis for one week, marked symptoms; March 2, after calcined magnesia and calcium carbonate only, no symptoms
			Feb. 25, p.m.	7.51*	74.0						
			Feb. 26, a.m.	7.53	74.0	...	334	9.6	35.3		
			Mar. 2, a.m.	7.41	55.1	550	303	....	30.8		
			Mar. 2, p.m.	7.39	59.8	560	312	14.1	36.4		
			April 22, p.m.	7.52*	68.3	556					
			April 23, a.m.	7.49*	63.6						
5. C. D.	43	M	Nov. 19, a.m.	7.52	76.8	519	...	15.2	....	21.2	Duodenal ulcer with slight obstruction. On November 19, marked symptoms before alkalis; November 26, no symptoms after routine alkalis for eleven days
			Nov. 26, a.m.	7.44	57.9	590	322				
			Dec. 7, a.m.	....	71.1	575	...	12.9	38.5		
6. C. S.	30	M	Nov. 16, a.m.	7.43	60.2	575	...	12.3	....	22.9	Duodenal ulcer with obstruction. November 16, before alkalis, no symptoms; November 30, after calcined magnesia and sodium carbonate only for four days, no symptoms; gastro-enterostomy, December 14
			Nov. 18, m.	7.39	60.7	594					
			Nov. 30, a.m.	7.52	73.0	588	361				
			Nov. 30, p.m.	7.49	72.1						
			Dec. 31, a.m.	7.29*	58.9	600	317	13.8	38.2		
7. W. W.	67	M	Nov. 25, a.m.	7.41	63.1	613	310	9.5	33.0	....	Gastric ulcer with slight obstruction. November 25, no symptoms before alkalis; November 30, marked symptoms after five days of alkalis; resection and gastro-enterostomy, December 7; entero-enterostomy, January 7
			Nov. 30, a.m.	7.50	68.3	550	290	9.8	33.8		
			Nov. 30, p.m.	7.52	77.7	512	306	9.0	38.7		
			Dec. 31, a.m.	7.45*	57.9	589	308	10.8	27.9		
			Feb. 5, a.m.	7.41*	51.3						

S. E. H.	27	M	Jan. 25, a.m.	7.46	67.3	577	324	14.7	39.3	....	Duodenal ulcer. Routine alkalis begun January 21; no symptoms of alkalosis
			April 21, p.m.	7.52*	69.2						
			April 22, a.m.	7.46*	61.7	613					
9. A. C.	75	M	Nov. 10, a.m.	7.40	48.5	...	...	....	....	....	Pyloric ulcer with marked obstruction. November 15, after five days calcined magnesia and calcium carbonate; moderate symptoms, November 22
			Nov. 15, a.m.	7.47	57.0	600	...	12.3	31.2		
			Nov. 22, a.m.	7.51	60.7	500					
			Dec. 6, a.m.	7.36	48.5	597	308	10.7	32.3	10.9	
			June 7	7.48*	59.8						
10. D. H.	70	M	Nov. 22, a.m.	7.51	72.1	550	...	7.3	....	22.5	Gastric ulcer, marked obstruction. Marked vomiting, no alkalis, moderate symptoms of alkalosis; died, Dec. 2, 1927
			Nov. 30, p.m.	....	65.5	550	300				
11. A. N.	42	M	Mar. 25, a.m.	7.45*	57.9	550	323	14.2	32.1	....	Gastric ulcer. Routine alkalis; March 25, 1927, no symptoms
			April 1, p.m.	(7.51*	64.5	600					
			April 2, a.m.	(7.43*	61.7						
12. L. O.	34	F	Nov. 10, a.m.	7.49	76.0	575	...	13.3	35.9	....	Duodenal obstruction, very marked obstruction. Routine alkalis from November 9 to 24, then stopped; moderate vomiting; mild symptoms of alkalosis
			Nov. 24, a.m.	....	65.5						
			Dec. 1, a.m.	7.43	68.3	600	307	12.4	31.4		
			Dec. 16, a.m.	7.51*	66.4	489					
13. O. J.	34	M	Mar. 8, a.m.	7.45*	68.3	550	306	13.8	37.5	....	Duodenal ulcer. March 8, after routine alkalis for eight days, no symptoms
			Mar. 8, p.m.	7.51*	74.0						
14. R. P.	20	M	Jan. 28, a.m.	7.44	74.0	563	343	14.1	30.6	....	Duodenal ulcer. January 28, after six weeks of routine alkalis; routine alkalis continued throughout entire period; no symptoms
			Feb. 17, a.m.	7.36	62.6	588	317	13.8	33.0		
			Mar. 12, a.m.	7.42*	61.7	...	...	14.6	31.9		
			Mar. 12, p.m.	7.43*	58.9						
			Mar. 25, p.m.	(7.50*	69.0						
			Mar. 26, a.m.	(7.38*	68.0						
			May 4	7.46*	59.8						
15. L. J.	39	M	Dec. 2, a.m.	7.49	74.9	550	322	15.2	33.5	15.5	Duodenal and gastric ulcer. Routine alkalis from November 30 to December 8, no symptoms of alkalosis; resection and entero-anastomosis, Dec. 10, 1926
			Dec. 31, a.m.	7.33*	64.5	525	283	....	28.0		
16. C. R.	55	M	Jan. 31, a.m.	7.42	57.0	600	306	10.9	30.9	....	Duodenal ulcer. Routine alkalis from February 1 to 5; no symptoms of alkalosis
			Feb. 5, a.m.	7.47	65.5	538	302	11.4	35.3		
			Feb. 14, a.m.	7.44*	65.5	600	323	10.6			
			Feb. 14, p.m.	7.49	73.0	550	350	10.1			
17. G. S.	54	M	Feb. 18, a.m.	7.38	58.9	588	337	12.3	35.7	....	Duodenal ulcer, slight obstruction. Calcined magnesia, 70 grains (4.5 Gm.) and calcium carbonate, 160 grains (10 Gm.); from February 2 to March 4, calcined magnesia, 70 grains; calcium carbonate, 80 grains (5.2 Gm.) and sodium bicarbonate, 310 grains (20 Gm.); no symptoms of alkalosis; Mosenthal test negative
			Mar. 2, p.m.	(7.39	65.5	540	306				
			Mar. 3, a.m.	(7.30*	59.8	631	313	12.8	36.3		
			Mar. 11, a.m.	(7.36	65.5	593	334	13.4	32.1		
			Mar. 11, p.m.	(7.49	74.9	502	325				
18. J. H.	41	M	Mar. 29, a.m.	7.37*	59.8	580	360	13.8	42.5	....	Duodenal ulcer. Routine alkalis from March 21 to discharge; no symptoms
			Mar. 30, p.m.	7.49*	69.2	575	...	13.5	38.7		
			Mar. 31, a.m.	7.49*	68.3						
			April 22, p.m.	7.54*	72.1						

* Determination made colorimetrically.

TABLE 1.—*Data on Acid-Base Balance of Blood in Patients with Peptic Ulcer Receiving Alkalis, Including Observations on Several Miscellaneous Conditions—Continued*

Case	Age	Sex	Date, 1926-1927	Electrometric p_H	Carbon Dioxide Content, Cc.	Plasma Chlorine as Sodium Chloride, Mg.	Serum Sodium, Mg.	Hemoglobin, Gm.	Nonprotein Nitrogen, Mg.	Urea Nitrogen, Mg.	Diagnosis; Comment
19. C. P.	35	M	Dec. 13, a.m.	7.48	75.8	...	...	....	....	....	Duodenal ulcer. Routine alkalis from December 3 to December 21, then none; no symptoms of alkalosis
			Dec. 31, a.m.	7.59	71.1						
20. J. J.	27	M	April 11, p.m.	{7.48*	81.5	...	...	....	....	....	Duodenal ulcer. After routine alkalis for eight days, no symptoms
			April 12, a.m.	{7.40*	72.1	581	...	15.0	31.9		
21. O. P.	34	F	May 12, 1925	7.44*	94.0	...	...	....	....	....	Duodenal ulcer, very marked obstruction. No alkalis except from May 8 to May 10; calcined magnesia, 75 grains, and calcium carbonate, 150 grains; moderate symptoms of alkalosis from May 10 to May 20; gastro-enterostomy May 22; all urine examinations negative
			May 20, 1925	7.48*	94.0	556	...	9.2	32.6	14.1	
			June 12, 1925	7.33*	56.0	...	...	7.4	....	20.0	
			June 20, 1925	7.29*	50.0	640	...	7.5	68.0	29.1	
			June 26, 1925	7.35*	52.0	...	...	7.6	46.2	27.4	
22. L. H.	36	M	Feb. 8, a.m.	7.43	63.5	613	322	14.6	38.7	....	Duodenal ulcer. February 10 to February 17, on calcined magnesia 50 grains, and calcium carbonate, 120 grains; February 18 to February 21, calcined magnesia, 50 grains, calcium carbonate, 60 grains, and sodium bicarbonate, 240 grains; no symptoms to February 18; severe headache, February 18 to February 21
			Feb. 17, p.m.	7.41	65.5	557	332				
			Feb. 18, a.m.	7.43	65.5	562	338				
			Feb. 21, p.m.	{7.46*	77.7						
			Feb. 22, a.m.	{7.39*	65.5						
23. C. L.	52	M	Nov. 24, a.m.	7.45	67.3	606	314	13.9	36.4	....	Duodenal ulcer. Routine alkalis from November 26 to December 17; no symptoms
			Dec. 13, a.m.	7.46	68.3	600	329	15.2	32 2	16.8	
24. J. L.	46	M	Dec. 13, a.m.	7.40	56.0	587	315	13.1	38.7	16.2	Duodenal ulcer, marked obstruction. Routine alkalis from December 14 to December 20, no symptoms
			Dec. 20, p.m.	7.46	71.8	575	300	13.2	45.4		
25. E. R.	27	M	Dec. 7, a.m.	7.46	72.1	560	328	13.3	36.1	....	Duodenal ulcer. After five weeks of routine alkalis, no symptoms
26. M. K.	26	M	Nov. 27, a.m.	7.46	61.7	590	311	14.3	41.7	....	Duodenal ulcer. After eight days of routine alkalis, no symptoms
27. R. L.	23	M	Nov. 9, a.m.	7.46	65.5	575	...	13.3	....	....	Gastric ulcer. Routine alkalis, November 9 to November 23; mild symptoms of alkalosis began November 22
			Nov. 15, a.m.	7.45	71.1	525	...	15.7			
			Nov. 23, a.m.	7.45	74.9	588	313				
28. W. W.	44	M	Feb. 28, p.m.	7.45	72.1	600	320	12.5	38.7	....	Duodenal ulcer. After six weeks of routine alkalis, no symptoms
29. F. H.	25	M	Mar. 16, a.m.	7.39*	66.4	...	...	14.9	38.7	....	Duodenal ulcer. Routine alkalis from March 9 to March 19, no symptoms
			Mar. 17, p.m.	7.45*	71.1						
30. E. W.	39	F	Feb. 14, a.m.	7.45	59.8	575	...	....	....	....	Duodenal ulcer. Routine alkalis for seven days; mild symptoms of alkalosis
31. E. W.	42	M	Mar. 31, p.m.	7.41*	62.6	600	...	15.2	32.3	....	Duodenal ulcer. Routine alkalis from April 1 to April 19; moderate symptoms of alkalosis after one week
			April 8, p.m.	{7.45*	72.1	...	...	13.2	28.8		
			April 9, a.m.	{7.39*	69.2						
			April 18, p.m.	{7.40*	69.2						
			April 19, a.m.	{7.34*	64.5	569					

32. H. A.	40	M	Jan. 25, a.m.	7.45	62.6	588	...	15.2	35.3	....	Duodenal and gastric ulcer. No alkalis; vomiting; slight symptoms of alkalosis
33. J. G.	53	M	Jan. 25, a.m.	7.45	60.7	600	315	12.3	28.6	....	Duodenal ulcer, moderate obstruction. January 25 after eight days of routine alkalis; mild symptoms of alkalosis, January 25 to January 27, before gastro-enterostomy
			Feb. 15, a.m.	7.40*	56.0	628	339	11.9	28.1		
34. M. S.	50	F	April 10, p.m.	7.43*	61.7	...	...	....	....	....	Duodenal ulcer. Calcium carbonate, 330 grains (23 Gm.), from April 11 to April 19; no symptoms of alkalosis
			April 11, a.m.	7.42*	54.1	619					
			April 18, p.m.	7.40*	64.5						
			April 19, a.m.	7.33*	62.6	594					
35. E. S.	47	M	June 16, 1925	7.43*	71.0	...	...	11.3	....	13.9	Duodenal ulcer, moderate obstruction. June 16, after ten days of routine alkalis, no symptoms; gastro-enterostomy, June 26
			June 30, 1925	7.41*	56.0						
			July 13, 1925	8.43*	57.0	...	...	11.0	27.6	8.0	
36. L. P.	35	M	Mar. 9, a.m.	7.41	57.9	575	312	14.9	38.7	....	Duodenal ulcer. March 9, before alkalis; routine alkalis, March 9 to discharge; no symptoms
			Mar. 16, a.m.	7.42*	68.3						
			Mar. 25	7.45*	57.0	588	...	13.8	28.8		
37. F. H.	26	M	Dec. 13, a.m.	7.41*	66.4	587	341	13.3	41.4	18.6	Duodenal ulcer. Routine alkalis, December 10 to December 15; no symptoms; gastro-enterostomy, December 20
			Dec. 20, a.m.	7.42	66.2	575	304	14.3	35.3		
			Dec. 31, a.m.	7.36*	67.3	550	314	13.8	32.1		
38. E. E.	35	F	Mar. 29	7.40*	48.5	588	...	12.9	27.0	....	Duodenal ulcer. Routine alkalis, March 31 to April 2, moderate symptoms of alkalosis; no alkalis, April 2 to April 8, then calcined magnesia, 50 grains (3.2 Gm.), and calcium carbonate, 120 grains (7.8 Gm.) daily, and less symptoms
			April 2, a.m.	7.40*	52.2						
			April 18, p.m.	7.40*	58.9						
			April 19, a.m.	7.41*	56.0	606					
39. G. W.	41	M	Mar. 18, p.m.	7.44*	59.8	562	326	14.2	35.9	....	Duodenal ulcer. From March 19 to discharge, calcined magnesia, 20 grains (1.3 Gm.) and calcium carbonate, 450 grains (29 Gm.); no symptoms
			Mar. 19, a.m.	7.40*	53.2	588	350	14.3	38.0		
			Mar. 30, p.m.	7.44	61.7	581	...	12.3	38.9		
			Mar. 31, a.m.	7.44	59.8						
			April 7, p.m.	7.41	61.7	563	...	13.9	42.2		
			April 8, a.m.	7.40	64.5						
40. E. W.	32	F	Feb. 6, a.m.	7.40*	68.3	556	329	....	....	....	Duodenal ulcer. After six weeks of routine alkalis, no symptoms
41. L. B.	58	F	Jan. 5, a.m.	7.39	59.8	545	312	14.1	36.4	....	Duodenal ulcer, marked obstruction. After five days of routine alkalis, moderate symptoms; only one kidney; phthalein and Mosenthal tests negative
42. W. B.	36	M	Jan. 6, a.m.	7.39	52.2	571	293	14.2	47.6	....	Duodenal ulcer, slight obstruction. After seven days of routine alkalis, no symptoms; phthalein and Mosenthal tests negative
43. M. W.	22	F	Feb. 11, p.m.	7.42*	66.4	...	...	....	....	....	Duodenal ulcer. Routine alkalis from February 7 to discharge; urine p_H, March 11, 7.3; no symptoms
			Mar. 10, p.m.	7.47*	60.7	600	325	12.5	35.3		
			Mar. 11, a.m.	7.45*	60.7	600	316	13.0	32.6		
44. M. W.	46	F	Feb. 8, a.m.	7.38	45.7	613	313	11.9	28.5		Duodenal ulcer. After seven days on calcined magnesia, 60 grains (3.9 Gm.) and calcium carbonate, 140 grains (9 Gm.), mild symptoms of alkalosis disappeared when alkalis were stopped
45. L. G.	26	M	April 21, p.m.	7.44*	63.6	...	...	....	....	....	Duodenal ulcer. After seven days of routine alkalis, no symptoms
			April 22, a.m.	7.39*	62.6	575					
46. C. H.	35	M	April 8, a.m.	7.34*	57.9	588	...	15.3	32.5	....	Duodenal ulcer, April 8, before alkalis. After ten days of alkalis, no symptoms
			April 18, p.m.	7.42*	71.1						
			April 19, a.m.	7.37*	67.3	600					

* Determination made colorimetrically.

TABLE 1.—*Data on Acid-Base Balance of Blood in Patients with Peptic Ulcer Receiving Alkalis, Including Observations on Several Miscellaneous Conditions—Continued*

Case	Age	Sex	Date, 1926-1927	Electrometric *pH*	Carbon Dioxide Content, Cc.	Plasma Chlorine as Sodium Chloride, Mg.	Serum Sodium, Mg.	Hemoglobin, Gm.	Non-protein Nitrogen, Mg.	Urea Nitrogen, Mg.	Diagnosis; Comment
								Miscellaneous			
47. J. H.	51	M	Feb. 26, a.m.	7.39	54.1	...	...	....	....	....	Carcinoma of stomach, pyloric obstruction. Vomiting from 750 to 1,000 cc. a day; no free acid
48. J. N.	71	M	Feb. 5, a.m.	7.40	54.1	569	333	14.1	38.9	....	Carcinoma of stomach, slight obstruction at pylorus. Irregular moderate vomiting
49. J. Z.	61	M	Feb. 14, a.m.	7.43*	51.3	550	320	5.6	37.5	....	Carcinoma of stomach, obstruction at pylorus. Moderate vomiting
50. P. S.	74	M	April 6, a.m.	7.49*	58.6	575	...	13.1	27.5	....	Carcinoma of stomach, obstruction. Slight vomiting
51. H. B.	63	M	April 6, a.m.	7.43*	35.1	575	...	6.3	35.3	....	Carcinoma of stomach, obstruction. Marked vomiting
52. H. K.	50	M	Nov. 27, a.m.	7.38	59.8	550	300	7.6	33.1	....	Carcinoma of stomach, cardiac end. Obstruction producing starvation
53. F. R.	52	M	Nov. 27, a.m.	7.47	55.1	550	312	12.2	45.5	....	Carcinoma of esophagus, producing nearly complete obstruction
			Dec. 1	7.45	59.8	575	311				
54. O. L.	58	M	Nov. 2, a.m.	7.46	....	606	...	12.1	....	18.6	General carcinomatosis. Marked emaciation
55. A. T.	71	F	Nov. 27, a.m.	7.49	57.0	600	355	12.5	41.1	....	Secondary carcinoma of liver. Jaundice the only symptom
			Dec. 1, a.m.	7.47	58.9	600	300	11.8	33.7		
56. J. G.	70	M	Jan. 31, a.m.	7.41	57.9	575	300	5.6	35.3	....	Carcinoma of the colon. Severe diarrhea
57. F. K.	32	M	Jan. 31, a.m.	7.39	57.9	538	313	14.2	37.5	....	Ulcerative colitis. Severe diarrhea, no other symptoms
58. C. C.	18	F	Feb. 26, p.m.	....	79.2	...	...	....	....	....	Nervous vomiting on admission; after 10 per cent dextrose and saline solution by rectum, sodium bromide, 240 grains (15.6 Gm.) daily, vomiting about stopped
			Mar. 9, a.m.	7.41	57.9	580	316	12.7	33.4		
59. E. C.	29	M	Oct. 26, a.m.	7.44	64.7	613	...	14.5	....	12.1	Nervous vomiting; headaches and drowsiness, relieved by dextrose and saline solution
			Nov. 1, a.m.	7.38	68.4	606	...	14.5	....	10.4	
60. J. E.	54	F	Mar. 7, a.m.	7.43	77.3	562	358	11.6	29.6	....	Postdiphtheritic neuritis, vomiting; symptoms relieved by intravenous and rectal 10 per cent dextrose and physiologic sodium chloride solution
61. T. C.	56	F	Nov. 13, a.m.	7.50	57.9	613	...	3.3	23.2	11 2	Pernicious anemia. No symptoms of alkalosis
62. L. D.	62	M	Jan. 31, a.m.	7.43	56.0	580	300	7.2	41.4	....	Pernicious anemia. Drowsy, vomiting
63. E. D.	23	M	Nov. 3, a.m.	7.40	66.0	606	...	9.4	....	27.4	Chronic diffuse nephritis, November 3, before medication. Calcium carbonate, 640 grains (22 Gm.) daily, from November 4 to November 27, no symptoms whatever; urine: albumin, 2+, average 1,000 cc.; hyaline and granular casts, 1+ to 2+; average blood pressure, 160/90; slight edema
			Nov. 9, a.m.	7.40	57.0	613	...	8.2	....	31.0	
			Nov. 16, a.m.	7.45	64.5	644	...	13.8	62.5		
			Nov. 27, a.m.	7.36	55.1	610	315				
64. J. S.	53	M	Nov. 12, a.m.	7.45	65.5	606	...	9.2	....	27.7	Chronic intestinal nephritis
65. L. W.	66	M	Nov. 12, a.m.	7.38	43.8	613	...	5.6	....	80.0	Chronic intestinal nephritis; creatinine, 11.1 mg.

* Determination made colorimetrically.

Clinically, one of us (W. E. G.) noted the symptoms and signs of alkalosis for a long time before he appreciated their significance or even suspected their cause. In a review of the end results in several hundred patients with peptic ulcer treated by the Sippy method,[19] it became evident that many discontinued the treatment shortly after leaving the hospital "because the powders made them sick." In our discussions with such patients, we have often felt that this was a matter of prejudice or distaste or only an inconvenience. Many such patients were considered neurotic and the headache, distaste for milk, subjective numbness and tingling of the hands and feet, aching of muscles and general "nervousness" were believed to be functional and independent of the treatment, even though the patients usually blamed the alkalis. In this study of individual patients under treatment we have been able to find, in at least a part of the cases, some changes in the blood which seem correlated with their clinical symptoms. We have also shown that these chemical changes could be produced by the alkalis and that the blood might become normal when the alkalis were stopped. In certain cases, there were other factors in addition to the powders which produced alkalemia. In some patients the intolerance to alkalis was only temporary, the disagreeable symptoms often disappearing without any change in the management. The study of the blood chemistry, followed in a number of cases over several months, indicates that the alkalemia may decrease or disappear after a time. In some cases the symptoms of alkalosis appear early, even within the first twenty-four hours when alkalis are administered, as in the Sippy routine. More commonly the symptoms and the changes in the blood chemistry appear much more gradually and either appear or become most marked after a week or ten days of the alkali treatment. If the symptoms have not appeared within the first two weeks of this management, they are not likely to become manifest later. To avoid clinical alkalosis and other complications in the medical treatment of persons with peptic ulcer, it has seemed advisable to keep all patients receiving the large doses of alkali under close observation, preferably in the hospital for at least two weeks. After this trouble in management was experienced, certain patients, particularly those with obstruction who had previously refused surgical treatment, finally agreed to allow the performance of an operation.

It is not our purpose here to discuss the relative merits of medical treatment with and without alkalis. In general, the Sippy form of management [19] was employed in the medical treatment of persons with peptic ulcer in this hospital. It is a widely used form of treatment,

19. Sippy, B. W.: Ulcer of the Stomach, Nelson's Loose Leaf Medicine **5**: 238, 1920.

but we do not believe that many physicians give sufficiently large doses of alkali to neutralize completely the free acid in the stomach. In the series of cases which we have studied, a consistent effort has not been made to control the free acidity so completely. The general principles of the Sippy management have been employed, hourly feedings with alkali powders having been given midway between the feedings and for four, or in some cases, five doses after the last feeding. The dose of alkali powder has been what may be termed the average dose as outlined by Sippy in his publications. In perhaps half of the cases studied, the free acid was completely neutralized. Rarely has the amount of alkali given in twenty-four hours exceeded the average or routine dose. In a few cases, when aspiration tests did not show free acid in the gastric juice, the dose was decreased. When an increase in the amount of alkali was made it was rarely in the form of soda but, as recommended by Sippy, in the form of calcium carbonate. The average total daily dose of magnesium oxide was about 45 grains (3 Gm.), of calcium carbonate, 100 grains (6.6 Gm.), and of sodium bicarbonate, 310 grains (20.6 Gm.). This dosage applies to the average patient receiving what may be best termed the routine management. As indicated in the table, certain variations were tried with a number of these patients in an effort to study the effect on the blood chemistry produced by or attributable to sodium bicarbonate and to calcium carbonate. Magnesium oxide alone without any other alkali could not be used in any case in sufficient quantity to approximate the neutralizing effect of the combined alkalis, and therefore the effect, if any, produced by magnesium oxide alone could not be studied. Only an occasional patient could take as much as 70 grains (4.6 Gm.) of magnesium oxide without producing intestinal cramps or diarrhea. In ten patients the effects of magnesium oxide and calcium carbonate, without sodium bicarbonate, were studied. Whenever sodium bicarbonate was omitted, enough calcium carbonate was given to neutralize the equivalent of the soda.

In those cases reported by Jordan [15] and also in those of Hardt and Rivers,[1] the patients were probably receiving on the average somewhat larger doses of alkali than the patients in our series, because an effort was made by them completely to neutralize the free hydrochloric acid, as was always recommended by Sippy.

In our study, especially in those patients showing symptoms of alkalosis, we have observed some changes in the blood chemistry and relief from symptoms when sodium bicarbonate was replaced by calcium carbonate. The only disagreeable result that we have ever noted clinically from the administration of calcium carbonate is the tendency to constipation with the formation of hard, dry and lumpy stools, a fecal impaction occasionally being produced. Recently, Loevenhart and Cran-

TABLE 2.—*Summary of Data on Patients with Peptic Ulcer Showing Disturbances of Acid-Base Balance*

Case	Age	Location of Ulcer	Obstruction	Alkali Administration	Symptoms of Alkalosis	Date, 1926-1927	*p*H	Carbon Dioxide Content, per Cent by Volume, Cc.	Plasma Chlorine as Sodium Chloride, Mg.
1. G. L.	53	Duodenum	Marked	No alkalis	Marked	Jan. 5, a.m.	7.6+	120	
						Jan. 24, a.m.	7.34	71	550
2. C. D.	66	Duodenum	None	Routine alkalis	Mild	Nov. 8, a.m.	7.55	79	572
3. R. P.	33	Duodenum	None	Routine alkalis	Marked	Dec. 13, a.m.	7.54	82	574
				Routine alkalis	Marked	Mar. 18, p.m.	7.50	58	550
4. D. B.	48	Duodenum	Slight	Routine alkalis	Marked	Feb. 26, a.m.	7.53	74	
				Routine alkalis	Marked	April 22, p.m.	7.52	68	
5. C. D.	43	Duodenum	Slight	No alkalis	Marked	Nov. 19, a.m.	7.52	77	519
				Calcined magnesia and calcium carbonate only	None	Nov. 23, a.m.	7.44	58	500
6. C. S.	30	Duodenum	Marked	Calcined magnesia and calcium carbonate only	Mild	Nov. 30, a.m.	7.52	73	588
7. W. W.	67	Stomach	Slight	Routine alkalis	Marked	Nov. 30, p.m.	7.52	78	512
8. E. H.	27	Duodenum	None	Routine alkalis	None	April 21, p.m.	7.52	69	
				Routine alkalis	None	April 22, a.m.	7.46	62	613
9. A. C.	75	Stomach	Marked	Calcined magnesia and calcium carbonate only	Moderate	Nov. 22, a.m.	7.51	61	500
10. D. H.	70	Stomach	Marked	No alkalis	Moderate	Nov. 22, a.m.	7.51	72	550
11. A. N.	42	Stomach	None	Routine alkalis	None	April 1, p.m.	7.51	65	600
12. L. O.	34	Duodenum	Marked	No alkalis	Mild	Dec. 16, a.m.	7.51	66	489
13. O. J.	34	Duodenum	None	Routine alkalis	None	Mar. 8, p.m.	7.51	74	
14. R. P.	20	Duodenum	None	Routine alkalis	None	Mar. 25, p.m.	7.50	60	
15. L. J.	39	Duodenum and stomach	None	Routine alkalis	None	Dec. 2, a.m.	7.49	75	550
16. C. R.	55	Duodenum	None	Routine alkalis	None	Feb. 14, p.m.	7.49	73	550
17. G. S.	54	Duodenum	Slight	Routine alkalis	None	Mar. 11, p.m.	7.49	75	502
18. J. H.	41	Duodenum	None	Routine alkalis	None	Mar. 30, p.m.	7.49	69	575
19. C. P.	35	Duodenum	None	Routine alkalis	None	Dec. 13, a.m.	7.48	76	513
20. J. J.	27	Duodenum	None	Routine alkalis	None	April 11, p.m.	7.48	82	
21. O. P.	34	Duodenum	Marked	Calcined magnesia and calcium carbonate only	Moderate	May 20, 1925	7.48	94	556

dall [20] have advocated calcium carbonate as the best antacid in the treatment of persons with peptic ulcer. From our study it seems evident that calcium carbonate is much less productive of alkalemia than sodium bicarbonate. It is obvious that if calcium carbonate and magnesium oxide are given in excess, this excess should not lead to the presence of free alkali, as in the case of sodium bicarbonate. Furthermore, the calcium chloride (and magnesium chloride) which is formed by the interreaction with hydrochloric acid in the stomach is probably in a large measure reconverted to some insoluble form, such as the carbonate or phosphate, in the intestine and the chloride ion reabsorbed. At any rate, this is what might be expected from the observations of Haldane, Hill and Luck [21] on the production of acidosis by the oral administration of calcium chloride.

CLINICAL SYMPTOMS AND VARIOUS CONDITIONS

The chief symptoms observed were headache, drowsiness, anorexia, nausea, vomiting, muscle-ache, nervousness and mental depression. Other less common nervous symptoms, such as a feeling of weakness and faintness, subjective "numbness" of the extremities, delirium, rapid and irregular respiration and marked irritability were also attributable to the alkalosis. The symptoms of nausea and vomiting occurring in patients with pyloric obstruction might be considered due to the obstruction and gastric irritability. When these symptoms paralleled other manifestations of alkalosis and increased with the administration of alkalis and with the alkalinity of the blood and subsided when the alkalis were stopped, it seemed likely that these gastric symptoms were at least in part due to the alkalosis. These symptoms occurred in some patients without obstruction when they did not exist before alkalis were given in large amounts. The muscle-ache was a fairly common symptom. Some complained of distress in the muscles of the back of the neck, or of pain in the calves of the legs and muscles of the arms, while others described the sensation as though their muscles were sore or as though they had an acute infection, such as influenza. Headache is a prominent and fairly constant symptom. In some instances, the headache was extreme and occurred in persons ordinarily not subject to headache. It was described by some as a feeling of great fulness and again, as if there were a band encircling the head. Drowsiness occurred as a well marked symptom in five patients and, at least in some instances, seemed independent of weakness. At times these patients would arouse

20. Loevenhart, A. S., and Crandall, L. A.: Calcium Carbonate in the Treatment of Gastric Hyperacidity Syndrome and in Gastric and Duodenal Ulcer, J. A. M. A. **88**:1557 (May 14) 1927.

21. Haldane, J. B. S.; Hill, R., and Luck, J. M.: Calcium Chloride Acidosis, J. Physiol. **57**:301, 1922-1923.

when addressed but would fall asleep at once, even before we left the bedside. They had to be aroused for food and medication. In the past, less well defined symptoms of "nervousness," depression, a feeling of marked weakness, tingling and "numb-feeling" in the extremities have been considered as functional and not attributable to any physical change in the patient. More careful observation convinces us that often these symptoms are directly due to alkalosis. After a few days they may disappear spontaneously.

Age.—As observed by Venables,[14] age seems to be a significant factor in the incidence of alkalosis in patients receiving alkalis. Definite symptoms as well as the changes that occur in the blood in alkalosis were observed in thirteen patients with ulcers. Their ages ranged between 33 and 75 years. Two were aged 36 and one, 33. The most marked symptoms occurred in a man, aged 53. He had a marked pyloric obstruction from a duodenal ulcer, but did not receive alkalis. The next most striking example of this phenomenon was seen in a man, aged 33, who had a duodenal ulcer that did not produce obstruction but who received alkalis that contained relatively large amounts of sodium bicarbonate. Neither of these patients had any recognizable renal damage. The younger of the two patients was so ill that on several occasions the alkalis had to be stopped altogether, but there would be a return of gastric distress when the alkalis were stopped and he refused operation. The older patient was treated surgically as soon as his general condition permitted. The average age of these thirteen patients presenting symptoms of alkalosis was 53 years. Four were women and nine were men. The average age of the entire group in this study was 40 years. Nine were women and thirty-seven were men.

Obstruction.—Well marked obstruction was present in six of the patients with typical symptoms of alkalosis. These patients usually received by rectal administration all of the 5 or 10 per cent dextrose in physiologic sodium chloride solution that they could retain and often several intravenous injections of this solution, especially when they were being prepared for operation. This treatment, no doubt, had considerable influence on the severity of their symptoms and the degree of alkalemia.

Nephritis.—Definite nephritis was not recognized in any of the patients who later developed alkalosis. Linder [22] pointed out that when considerable renal insufficiency is present, there is evidence of failure to adjust the acid-base balance with the customary delicacy. It has been known for some time that persons with an advanced form of chronic

22. Linder, G. C.: The Effect of Mineral Acid on Acid-Base Regulation in Health and Nephritis, Quart J. Med. **20**:285 (April) 1927.

interstitial nephritis invariably suffer from an acidosis.[23] We did not see any evidence of renal damage resulting from the use of the alkalis in this series of cases. One patient, a woman, aged 48, had a slight hematuria for a day or two at a time when she also had symptoms of alkalosis, but there was no other evidence in the urine or in the blood chemistry of renal damage. In one patient in whom a nephrectomy had been performed five years before our observation, evidence of renal insufficiency was not found at any time. In a considerable number of cases, routine determinations of phenolsulphonphthalein were made, all of which were normal. Frequent chemical and microscopic examinations of the urine did not show evidence of nephritis. There were slight elevations in nonprotein nitrogen in the blood, but none of the cases studied showed any marked retention.

One patient, case 63 in the miscellaneous group at the end of table 1, who did not have an ulcer or any other gastro-intestinal condition but who was under treatment for a chronic diffuse nephritis, was given calcium carbonate in large doses for several days, chiefly to determine if in this person with a well defined nephritis an alkalosis would result. A change was not produced in the renal efficiency, at least during our period of observation. He did not suffer any inconvenience and we did not note any change in his general condition. The protein intake was restricted to 40 Gm. and the diet was "salt-free." He had slight edema both before the administration of the calcium carbonate and while receiving it, and there was no appreciable variation in the edema or in the fluid output.

Tetany.—In none of our patients was tetany observed. At times, when handling patients with marked obstruction and intense vomiting, we have noted this phenomenon but have not made a study of the blood chemistry in such cases as in the group here described. The occurrence of tetany in patients with alkalosis has been discussed by McVicar[13] and in the reports from Guy's Hospital by Hurst, Houghton, Venables and Lloyd.[14]

The Appearance of Symptoms.—We were interested in seeing how quickly the effects of the alkalis on the blood might appear and disappear. In some instances the first symptoms, usually headache and anorexia, appeared as early as the third day of alkali therapy. Less definite evidence of alkalosis, accompanied by a fairly definite alkalemia, may occasionally occur on the first day. Usually the well defined symptoms of alkalosis did not appear until from the sixth to the eighth day. Often the milder symptoms disappeared entirely without any change in the treatment. It was noted that when symptoms did occur they

23. Chace, A. F., and Myers, V. C.: Acidosis in Nephritis, J. A. M. A. **74**:641 (March 6) 1920.

TABLE 3.—*Data on Patients Showing Alkalosis of the Late Afternoon*

Case	Age	Ulcer	Obstruction	Alkalis: Calcined Magnesia	Alkalis: Calcium Carbonate	Alkalis: Sodium Bicarbonate	Symptoms	Date, 1926-1927	p_H	Carbon Dioxide Content, per Cent by Volume, Cc.	Plasma Chlorine as Sodium Chloride, Mg.
3. R. P.	33	Duodenal	None	50 grains (3.2 Gm.)	80 grains (5.2 Gm.)	290 grains (19 Gm.)	Marked	Feb. 11, 5:10 p.m.	7.50	75	563
								Feb. 11, 8:45 a.m.	7.43	50	504
				20 grains (1.3 Gm.)	280 grains (18.2 Gm.)	0	None	Mar. 18, 5:00 p.m.	7.50	58	550
								Mar. 19, 8:30 a.m.	7.39	53	569
4. D. B.	48	Duodenal	Slight	30 grains (1.9 Gm.)	110 grains (7 Gm.)	360 grains (23.3 Gm.)	None	April 22, 8:00 p.m.	7.52	68	556
								April 23, 7:00 a.m.	7.46	64	
6. C. S.	30	Duodenal	Marked	20 grains (1.3 Gm.)	600 grains (39 Gm.)	0	None	Nov. 30, 6:15 a.m.	7.52	73	588
								Nov. 30, 6:45 p.m.	7.49	72	
8. E. H.	27	Duodenal	None	30 grains (1.9 Gm.)	110 grains (7 Gm.)	360 grains (23.3 Gm.)	None	April 21, 4:50 p.m.	7.52	69	
								April 22, 7:40 a.m.	7.46	62	613
13. O. J.	34	Duodenal	None	20 grains (1.3 Gm.)	130 grains (8.4 Gm.)	410 grains (26.6 Gm.)	None	Mar. 8, 6:40 a.m.	7.45	68	550
								Mar. 8, 6:40 p.m.	7.51	74	
16. C. R.	55	Duodenal	None	70 grains (4.5 Gm.)	80 grains (5.2 Gm.)	310 grains (20 Gm.)	None	Feb. 14, 6:50 a.m.	7.44	66	600
								Feb. 14, 6:30 p.m.	7.51	73	559
17. G. S.	54	Duodenal	Slight	70 grains (4.5 Gm.)	80 grains (5.2 Gm.)	310 grains (20 Gm.)	None	Mar. 11, 6:20 a.m.	7.36	66	593
								Mar. 11, 6:30 p.m.	7.49	75	562
22 L. H.	36	Duodenal	None	50 grains (3.2 Gm.)	60 grains (3.9 Gm.)	230 grains (14.9 Gm.)	Marked	Feb. 21, 6:30 p.m.	7.46	78	
								Feb. 22, 6:40 a.m.	7.39	66	
7. W. W.	67	Gastric	Slight	60 grains (3.9 Gm.)	70 grains (4.5 Gm.)	270 grains (17.5 Gm.)	Quite marked	Nov. 30, 6:30 a.m.	7.50	68	550
								Nov. 30, 6:50 p.m.	7.52	78	512

increased during the day when alkalis were administered. The patients who had severe headache might feel well in the morning but by 3 or 4 o'clock in the afternoon would have a raging headache. When the treatment was continued, this might be a daily occurrence. The blood became more alkaline at the end of the day when the routine determinations of alkali were being taken and as a rule returned to a more normal condition in the morning before the administration of the alkalis was resumed (table 3).

LABORATORY AND CLINICAL STUDY

The analyses of the blood included estimations of the p_H, both colorimetrically and electrometrically, the carbon dioxide content, the plasma chloride, the serum sodium and the inorganic phosphorus of the serum or plasma, in addition to such more or less routine analyses as those of the hemoglobin, nonprotein and urea nitrogen, uric acid, creatinine and sugar. For the determination of the p_H, carbon dioxide content and chlorides, oxalated plasma separated under oil was employed. Electrometric determinations of the p_H were carried out at 38 C. and the colorimetric determinations at room temperature and corrected to 38 C. The technic employed for these determinations has been briefly described elsewhere by Myers and Muntwyler.[24] The Van Slyke-Stadie [25] method was employed for the carbon dioxide, the Myers-Short [26] method for the chlorides and the Kramer-Tisdall [27] method for the sodium. (Although we were able to obtain quantitative recoveries with added sodium, our results appear to be a little low. It is believed, however, that they are comparable.) As a routine, all of the blood specimens were taken in the early morning (from 6 to 7 a. m.) before food or alkali had been given, obviously at a time unfavorable for the detection of a mild alkalemia. As has been pointed out by some authors, there are likely to be minor changes in the blood reaction after the ingestion of a meal, as hydrochloric acid is secreted in considerable quantity into the stomach. In persons with obstruction or marked hypersecretion, this accumulation of acid in the stomach and consequent shift of acid-base equilibrium may be independent of the administration of alkalis. In order to bring out the influence of alkali

24. Myers, V. C., and Muntwyler, E.: The Colorimetric Estimation of the Hydrogen Ion Concentration of Blood, J. Biol. Chem. **78**:243 (June) 1928.

25. Van Slyke, D. D., and Stadie, W. C.: The Determination of the Gases of the Blood, J. Biol. Chem. **49**:1, 1921.

26. Myers, V. C., and Short, J. J.: The Estimation of Chlorides in Blood, J. Biol. Chem. **44**:47 (Oct.) 1920.

27. Kramer, B., and Tisdall, F. F.: A Simple Method for the Direct Quantitative Determination of Sodium in Small Amounts of Serum, J. Biol. Chem. **46**:467, 1921.

administered during the day, the blood specimens were again taken in the late afternoon or early evening in some cases. In most of the cases studied, determinations were made before any alkalis were administered and again after a week or more of treatment with alkalis.

About two thirds of the patients with ulcer studied at some time showed either a high bicarbonate value or p_H or both. Of these, twenty-one cases (out of the total of forty-six cases) showed an uncompensated alkalosis, if electrometric p_H values of 7.48 or above may be taken as a reliable guide. Some of the more pertinent figures in these cases are summarized in table 2. Four of the twenty-one cases (3, 9, 11 and 12) with high p_H values gave normal figures for carbon dioxide content (from 58 to 66 per cent by volume), and might have been missed, if the determination of p_H had been omitted. Seventeen of the patients (table 1) with carbon dioxide contents ranging from 68.3 to 94.0 per cent by volume gave p_H readings ranging from 7.39 to 7.46 and therefore at the time of these determinations belonged to the compensated variety of alkalosis.

It has been recognized for some time that with the marked rise in blood bicarbonate in "high up" intestinal obstruction there is a corresponding fall in the plasma chloride. Jordan [15] called attention to a similar change after the administration of sodium bicarbonate. This change stands out strikingly in our series of cases. A group of ten unselected patients with high figures for carbon dioxide content give an average plasma chloride of 558 mg. per hundred cubic centimeters, as compared with an average of 591 mg. from fifteen analyses made in persons with normal carbon dioxide content, a difference of 33 mg. It is of further interest that the patients with high figures for the carbon dioxide content but low plasma chloride showed an average of 327 mg. of sodium per hundred cubic centimeters of serum, compared with 311 mg. for the other series of cases.

Clinically, as has often been observed by others, we noted the disagreeable symptoms of alkalosis most commonly when the plasma chloride was low and saw a marked improvement in the general condition of the patient when sodium chloride was administered, especially by the intravenous route. This procedure should be employed as a routine in the preparation of patients with pyloric obstruction for operation.

Somewhat less than half of the patients exhibiting an alkalemia of either the compensated or uncompensated variety showed a slight elevation in the nonprotein or urea nitrogen. There did not appear to be any relationship between this and the severity of the alkalosis, however.

Eight patients (cases 1, 6, 7, 15, 21, 33, 35 and 37 in table 1) with pyloric obstruction were studied before and after operation. In general, patients with pyloric obstruction, especially if it is of high grade, are

transferred promptly to surgical treatment if they will consent to operation. Before operation they are prepared in accordance with the principles outlined by Berkman.[28] In several of these patients with obstruction, operation was absolutely refused and it was necessary to treat them medically. In most of those patients with obstruction and well marked alkalosis before operation, the blood chemistry became essentially normal after removal of the obstruction. In the patient with pyloric obstruction who is either vomiting large amounts or is having frequent aspiration and gastric lavage, the loss of large quantities of acid in the gastric juice and the failure of adequate amounts of chloride to reach the small bowel lead to alkalosis. The administration of alkalis, particularly sodium bicarbonate, to such patients, as is frequently done if they have the characteristic ulcer pain, further increases the alkalosis. There is little doubt that soda should be withheld from these patients, and that either calcium carbonate or magnesium oxide or combinations of these two alkalis may be given with much greater safety. As an essential part of their treatment water and salt must be supplied either by rectum or, if necessary, intravenously or subcutaneously. In some of these patients who are dehydrated and who have alkalosis, unusual skill and effort are necessary to supply these two simple but important substances, water and salt. The veins are often so collapsed that the ordinary injections are difficult. The dextrose added to the solution is probably of considerable value in supporting the strength of the patient. In the postoperative period much may be done to save the life of such patients by continuing to supply an abundance of water and salt.

Gamble and McIver [29] indicated that the content of chloride in gastric juice is fairly constant and approximates that of the blood plasma. If the gastric juice vomited by the patient with pyloric obstruction contains this concentration of chloride, it is readily seen that the depletion of the plasma chlorides is rapid when a liter or two of the juice is being vomited each day. Ramos and Fox [30] directed attention to the rôle of water in maintaining the acid-base equilibrium and considered that dehydration promotes acidosis. Koehler [16] and others discussed the effect of starvation in producing acidosis. It seems that some of these factors, in patients with obstruction and vomiting, counteract others. The effect of dehydration and starvation may in part reduce the alkalosis. The determinations concerning the blood chemistry only serve as a partial indication of the resulting balance, or imbalance.

28. Berkman, D. M.: Preoperative Management in Cases of Gastric Retention, M. Clin. N. Amer. **5**:411 (Sept.) 1921.

29. Gamble, J. L., and McIver, M. A.: Fixed Base in Gastric Juice, Proc. Soc. Exper. Biol. & Med. **23**:439, 1926.

30. Ramos, S., and Fox, G. L.: Rôle de l'eau dans le maintien de l'equilibre acido-basique du sang, J. de physiol. et de path. gén. **24**:231 (April) 1926.

REPORT OF CASES

CASE 1.—G. L., aged 53 years, admitted to the hospital, Dec. 27, 1926, had the typical symptoms and roentgen-ray evidence of a chronic duodenal ulcer producing almost complete obstruction. He had vomited large quantities of watery material for about ten days and had rapidly become weak. In the past two months he had lost about 25 pounds (11.3 Kg.). In addition to the usual acid type of distress and unusual gastric hyperperistalsis, of which he was conscious, he complained of marked thirst, dryness of the mouth, and at the same time nausea, anorexia and vomiting independent of the abdominal discomfort. He volunteered the complaint of a steady dull headache which had been present for several days, and mentioned that his muscles were sore, "as if he had been pounded." He was noticeably apathetic and drowsy. He was vomiting several times a day, and the balance indicated that the quantity of vomitus was greater than his total fluid intake. The urine was scanty and contained a bare trace of albumin and a few hyaline casts. At times a single emesis would amount to between 1,000 and 1,500 cc. In two specimens of vomitus, the free acid was 30 and 27 and the total acid, 45 and 52. It was difficult to puncture a vein either to obtain blood for examination or to give intravenous salt solution. The blood specimen obtained on Jan. 5, 1927, which was a few days after his most critical period, gave the highest p_H value that we have noted at any time in this entire study. The value of 7.6 "plus" is assigned, as the specimen exceeded even that figure in alkalinity, a standard not being immediately available to compare with this surprisingly alkaline blood. The carbon dioxide content of the plasma was also extraordinary, 120 cc. per hundred cubic centimeters of plasma. The specimen was too small to determine the p_H electrometrically or to make the other routine determinations.

This patient had not received alkalis for some time before admission and none after admission to the hospital. He was given by rectum all of the normal salt solution containing 5 per cent dextrose that he could retain; twice, he was given about 800 cc. of physiologic sodium chloride solution intravenously and smaller amounts subcutaneously. The stomach was washed out each night. It was impossible for us to get satisfactory specimens of blood again before operation. He was sufficiently improved so that gastro-enterostomy was performed on Jan. 12, 1927. He had been stuporous, almost comatose, and evidently near death for a number of days and after the operation his condition was not satisfactory for ten days but by January 24, he was decidedly improved. The carbon dioxide content of the plasma was then 71.1 cc. and the plasma chlorides, 0.55 per cent. The patient made a complete recovery.

CASE 6.—C. S., a negro, aged 30 years, with symptoms of a duodenal ulcer and roentgen-ray evidence of duodenal deformity, had been admitted to the medical service and after three weeks of instruction in the use of the Sippy management had been discharged with directions to continue the treatment. His monthly reports indicated that he was not getting along well. At his first admission there was no evidence of obstruction. He returned six months later with vomiting, visible peristalsis and evidence of obstruction. He vomited large amounts of gastric juice, and retained food, but only infrequently. During this second admission, while he was in the medical department prior to operation, the stomach was aspirated and washed each night, from 500 to 2,000 cc. being obtained, the average amounting to about 1,100 cc. He was not given alkalis for ten days and on Nov. 26, 1926 (table 1), was placed on magnesium oxide and calcium carbonate, without any sodium bicarbonate. The average total daily dose was 20 grains (1.3 Gm.) of magnesium oxide and 600 grains (39 Gm.) of calcium

carbonate. The alkalis were discontinued four days before operation, and the usual preoperative measures for increasing the supply of salt and water were employed. For more than a month he had refused operation but finally consented, and a gastro-enterostomy was done on December 14. He made an uneventful recovery. Seventeen days after operation, the blood was normal. At no time were there any definite symptoms of alkalosis. Although the analyses of the blood indicated moderate alkalemia and some chloride deficit, his condition was not materially altered by the use of the alkalis when soda was excluded. The removal of the obstruction relieved the alkalemia.

CASE 21.—O. P., a woman, aged 34 years, presented the clinical picture of a duodenal ulcer with marked obstruction. By vomiting and aspiration of the stomach, she was losing from 650 to 3,000 cc. of gastric content daily, on the average, about 1,500 cc. She complained some of headache, nervousness and muscle-ache in addition to anorexia, nausea and vomiting. While we waited for her consent to operation, the treatment was chiefly the furnishing of physiologic sodium chloride solution by bowel, aspiration and lavage of the stomach each night, and a soft diet three times a day. For two days only she received alkalis, about 75 grains (4.9 Gm.) of magnesium oxide and 150 grains (10 Gm.) of calcium carbonate, without soda. On account of the recognized alkalosis, these were used only for the two days. The analyses in the table indicate the marked alkalemia and low blood chloride content, due to the obstruction and vomiting rather than to the alkalis. The change in the blood chemistry after the removal of the obstruction is remarkable.

CASE 7.—W. B. W., a man, aged 67 years, was admitted to the hospital with a diagnosis of gastric ulcer with slight obstruction. He had lost considerable weight and had vomited moderately. He was advised to have surgical treatment but did not accept this advice for several days. He was placed on hourly feedings but without alkalis at first. At this time, definite symptoms attributable to alkalosis were not present. Because of severe distress he was placed on the routine alkalis on Nov. 25, 1926, and these were continued until Dec. 5, two days before operation. He received on the average about 50 grains (3.3 Gm.) of heavy magnesium oxide, 270 grains (17.6 Gm.) of sodium bicarbonate and 70 grains (4.6 Gm.) of calcium carbonate a day. On November 29, four days after the alkalis were started he began to complain of headache and muscle-ache, and on the fifth day there were pronounced symptoms of alkalosis with anorexia, nausea, vomiting, muscle-ache, apathy and marked drowsiness. On this date the blood chemistry showed a marked change rather directly attributable to the alkalis. The blood had been essentially normal five days before, or at the time the use of alkalis was started, and now there were pronounced alkalemia, a considerable increase in the carbon dioxide content of the plasma, especially at the end of the day, and a marked fall in the plasma chlorides. On account of the pain this patient continued to receive alkalis, though somewhat less sodium bicarbonate, until he consented to have the operation. In general, we have noted that there is more satisfactory relief from pain when soda is used than is secured from the other alkalis.

Because we believed that sodium bicarbonate contributed more to the production of alkalemia than the other alkalis used in the Sippy treatment, we made some effort to determine the effects of the alkalis when soda was omitted. Clinically, some of those patients who complained while they were being given the routine alkalis became com-

fortable when the soda was replaced by an equivalent of the other alkalis. Some of the patients were given only magnesium oxide and calcium carbonate for a control period and then for about a week were placed on the routine alkalis containing the sodium bicarbonate. Analyses of the blood were made at the beginning and end of this period. In some of these patients, although an appreciable alkalemia developed after soda was given, disagreeable symptoms attributable to alkalosis did not occur. In other patients, this change in the alkalis produced the usual symptoms of alkalosis (cases 3, 4, 5, 9, 17, 22, 34 and 39 in table 1).

CASE 3.—R. P., with an uncomplicated duodenal ulcer, began to have symptoms attributable to the alkalis after he had followed the routine (including sodium bicarbonate) for three days. He complained of a dull, steady headache at first, although he could scarcely recall having had a headache before. He complained of nervousness and difficulty in remaining quiet in bed, and stated that everything and everybody annoyed him. His muscles ached as if he were "coming down with influenza." He developed a distaste for milk and cream and for other articles of soft diet. He preferred to be left alone and wanted the treatment stopped in the midafternoon. In the mornings he would feel better and practically free from the headache. Each day these symptoms seemed to grow worse. He questioned the benefits to be derived from such treatment. Finally the alkalis were temporarily discontinued and he felt all right. He was discharged from the hospital on alkalis but without any sodium bicarbonate. At the end of six weeks he was again placed on the routine alkalis (including sodium bicarbonate) and again had the same train of symptoms, the headache being the most troublesome. The blood chemistry determinations of February 11 and 12 indicate a fairly severe alkalosis as the cause of these symptoms. It seemed of especial interest to note that the alkalemia was less in the morning at the time when his symptoms were least marked. The average daily dose of the alkalis while he was on the routine treatment was 50 grains (3.3 Gm.) of magnesium oxide, 80 grains (5.2 Gm.) of calcium carbonate and 290 grains (19 Gm.) of sodium bicarbonate. When the soda was omitted he received as the average daily dose 20 grains of magnesium oxide and 280 grains (18 Gm.) of calcium carbonate, and this represents a 10 per cent greater neutralizing value. This patient has continued the management without soda for five months and has not had further trouble.

CASE 22.—L. H., a man, aged 36 years, with an uncomplicated duodenal ulcer, did not have symptoms of alkalosis until he was placed on powders containing sodium bicarbonate. On February 8, before he took any alkalis, his blood chemistry was essentially normal. From February 10 to the 17, inclusive, he took as the average daily dose 50 grains (3.3 Gm.) of magnesium oxide and 120 grains (7.8 Gm.) of calcium carbonate. During this period the only important change noted in the blood chemistry was the fall in the plasma chlorides. On February 18 he began to take soda, the average daily dose of alkalis in the next three days being 50 grains (3.3 Gm.) of magnesium oxide, 60 grains (3.9 Gm.) of calcium carbonate and 230 grains (15 Gm.) of sodium bicarbonate. The neutralizing value of this combination is about the equivalent of 80 grains (5.2 Gm.) of soda more than the previous dosage. At 4 o'clock on the first afternoon that soda was given he began to have severe headache and this continued each day until the soda was stopped; the headache was less intense in the morning but increased

in the late afternoon. The urine on the third day of this treatment had a p_H of 7.85 at noon, of 7.90 at 3 p. m. and of 7.95 at 6 p. m. This patient was discharged on alkalis not containing sodium bicarbonate and he has not had a return of alkalosis.

Previous to making the study of the blood chemistry in this group of cases, one of us (W. E. G.) noted that patients might feel well in the morning but might complain of distaste for the milk, nausea, headache, drowsiness and general dislike of the management by the middle or latter part of the afternoon. Some patients would omit the last two or three hours of their management. We attributed this to a number of different things—distaste for the powders, dislike for the milk, souring of the milk (although the nurses and other patients assured us that the milk was sweet) or, finally, to lack of cooperation on the part of these patients. In this study we have seen some interesting changes in the blood chemistry between morning and night, when alkalis were given, and between night and morning as the patient excreted, the excess of alkali tending to restore the acid-base equilibrium to normal.

This is well illustrated by the data summarized in table 3. It will be noted that the p_H and carbon dioxide content are always higher and the plasma chloride lower in the evening than in the previous or following morning, the only exceptions being patients in whom the alkalosis was severe. In such instances, the time interval does not appear to be great enough to allow compensation.

In a few instances, not recorded, the p_H of the urine was followed, but in all of these cases the kidneys were apparently readily able to excrete alkali. As pointed out by Myers and Booher,[31] patients whose kidneys do not readily secrete an alkaline urine tolerate alkalis poorly.

ACID-BASE BALANCE IN SOME MISCELLANEOUS CONDITIONS

The study of the blood chemistry has been somewhat extended to include other conditions which to us seem related.

The first group to which we wish to call attention, the patients in cases 47 to 52, were all suffering from carcinoma of the stomach. None of these patients had symptoms of alkalosis. In two instances, cases 50 and 52, there was alkalemia, as indicated by the determinations of p_H. In all of these six patients, the carbon dioxide content of the plasma was normal or subnormal and in all in whom the plasma chlorides were determined there was a chloride deficit. In three patients with considerable secondary anemia, as indicated by the low hemoglobin content of the venous blood, a deficient oxygen carrying power of the blood may have had something to do with the carbon dioxide content and reaction of the plasma.

In patients with carcinoma of the stomach, there are a number of factors which disturb the blood chemistry. When obstruction is present at the cardiac

31. Myers, V. C., and Booher, L. E.: Observations on the Excretion of an Acid Urine in Alkalosis, Proc. Soc. Exper. Biol. & Med. **22**:513, 1925.

end of the stomach or in the esophagus, probably the chief factor is the failure to ingest sufficient water, food and salt so that eventually there is a chloride deficit and a tendency to acidosis. With an obstruction at the pylorus, there is the additional factor of the loss of water and secretions from the stomach itself. Some patients, in whom the gastric juice has remained fairly normal with large quantities of free acid in the stomach, may present the same general picture as that of a benign ulcer at the pylorus with obstruction. The patient in case 10 during life was supposed to have had a carcinoma of the stomach with pyloric obstruction and the condition was thought inoperable. Postmortem examination revealed a large ulcer which had perforated at some time, probably months before our examination, the floor of the ulcer being formed by the anterior surface of the pancreas. On account of the patient's age, the extent of the pathologic change and the poor general condition, it is doubtful if surgical treatment would have offered him much benefit. However, in our review of this case, we realize that we should have employed the administration of physiologic sodium chloride solution and water more diligently.

Although the gastric juice of patients with carcinoma of the stomach often contains little if any free acid, there is reason to believe that the chloride content of this juice is nearly normal. Vomiting of large quantities of gastric juice by these patients may result in a depletion of the plasma chloride, though it is less productive of alkalemia than in those patients with peptic ulcer in whom the acid values are normal or increased.

Cases 52 and 53 are much alike in our consideration, because the blood chemistry is probably altered chiefly by the restricted intake and the resulting starvation and dehydration.

Cases 54 and 55 are tabulated for comparison with the other cases of carcinoma. The patients had late and rather generalized carcinomatosis without any recognized involvement of the digestive tube. Naturally their food and fluid intake was somewhat abnormal.

The patients in cases 56 and 57 who show little change in the elements of the blood which we studied, except a fall in the plasma chlorides, had severe diarrhea. Because they were severely ill their food intake was less than normal. The fluid intake was above normal, but the loss was sufficient to produce some dehydration.

Cases 58, 59 and 60 are grouped together because none of these patients had any evidence of organic disease of the gastro-intestinal tract nor disturbance of the gastric secretions. At the time of admission, only the carbon dioxide determination was made in case 58. We believe that the p_H was probably high at that time and that the plasma chlorides were much lower than when determined about two weeks later after the girl had been treated. Her history indicated that she had vomited "almost everything" for weeks before admission. Because of her obvious neurosis, we did not know how many of her symptoms and complaints were due to the general nervous condition and how many were due to an alkalosis resulting from the prolonged vomiting or regurgitations. In case 60 the vomiting occurred almost immediately after any food or drink was taken and the patient became extremely emaciated. We had a great deal of difficulty in supplying adequate nourishment and fluids but ultimately succeeded in getting her up and about.

The patients in cases 61 and 62 vomited a great deal in the terminal stages of pernicious anemia. It would be difficult to tell how many of their symptoms were due to the nervous manifestations of the disease and failing strength and how many were due to the vomiting. So far as we know the actual chloride

content of the gastric juice in such cases has not been determined. The absence of free acidity would probably lessen the tendency to alkalosis when severe vomiting occurs in such cases, and there are factors which would tend to produce acidosis.

The patients in cases 63, 64 and 65 had chronic nephritis. The patient in case 63, previously mentioned, received larger doses of calcium carbonate than would ordinarily be administered to control gastric acidity. Our purpose was to note any untoward effects produced by the calcium carbonate in a patient who was known already to have advanced nephritis. We did not note any disagreeable effects. There was no apparent disturbance of the acid-base equilibrium. We obtained normal or slightly elevated values for the plasma chlorides, which may have depended on the diffuse or mixed nephritis. We did not feel justified in repeating this test with the substitution of sodium bicarbonate for the calcium carbonate. The nephritis was of the chronic interstitial type in both case 64 and case 65, and neither of these patients received alkalis.

Naturally, we cannot establish many facts from this small group of miscellaneous cases but mention them because of their similarity to certain cases of peptic ulcer complicated by vomiting, obstruction, anemia and nephritis.

CONCLUSIONS

A series of forty-six patients with gastric or duodenal ulcer has been studied, with particular reference to the acid-base balance. A definite correlation between the alkalemia in these cases and a group of clinical symptoms that are chiefly nervous in character has been observed. About two thirds of these patients at some time showed a high carbon dioxide content or p_H or both, and twenty-one showed an uncompensated alkalosis, if electrometric p_H values of 7.48 or above may be taken as a reliable guide. Pyloric obstruction is obviously an important factor in the production of alkalosis. The surgical relief of the pyloric obstruction restores the acid-base balance and the chloride deficit in these cases.

When used in such amounts as are commonly employed in the treatment of peptic ulcer by the Sippy method, the alkalis almost always produce characteristic changes in the blood chemistry, even though the symptoms of alkalosis may not occur. When calcium carbonate and magnesium oxide are employed without the use of soda in this management, alkalemia is decidedly less severe and the clinical symptoms of alkalosis are unlikely to appear, especially if the complication of obstruction or vomiting does not occur. The changes produced by the alkalis are most marked at the end of the day, and during the night the condition tends to return to normal.

In this limited series of cases, there was no definite evidence that the alkalemia in the degree observed by us was productive of any renal damage.

With the rise in the blood bicarbonate, there is a corresponding fall in the plasma chlorides. The rise in the bicarbonate appears to be accompanied in many cases by a slight rise in the serum sodium.

The clinical symptoms of alkalosis are again briefly described. Many of the symptoms which have previously been considered as functional are due to a disturbance in the nervous system secondary to the alkalemia.

The importance of administering water and sodium chloride to patients suffering from alkalosis and especially as a preoperative and postoperative measure seems obvious but is again emphasized. When patients who have been receiving alkalis as a part of the treatment for ulcer consent to operation, the alkalis should be omitted for at least several days before the operation. During this interval, the usual methods of forcing water and salt should be employed.

A miscellaneous group of nineteen cases has been discussed in connection with the alkalosis occurring in the treatment of persons with peptic ulcer because some of these conditions have similar features producing changes in the blood chemistry. The number of cases in any particular group was insufficient to warrant any general conclusions concerning the blood chemistry of such a group as a whole.

TOTAL CHLORIDE CONCENTRATION AND ACIDITY OF THE GASTRIC CONTENTS

A COMPARATIVE STUDY *

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ST. LOUIS

Various procedures have been recommended for measuring gastric secretion in man. Certain English investigators [1] have suggested that the total chlorides of a sample of contents of the stomach as determined by the direct Volhard method, after filtration but without ashing, is more accurate than the acidity as an index to the amount of gastric secretion, because much or little of the acid secreted may have been neutralized. They state further that a comparison of the acidity, as determined by the Toepfer method, and the total chlorides gives information as to the amount of neutralization that has occurred. However, this depends on the hypothesis that the chief source of the chlorides in the stomach is hydrochloric acid, an assumption of fundamental importance and one worthy of investigation.

In this paper, we report the results of a comparative study of the total chloride concentration and acidity of the gastric contents in a series of cases presenting both normal and abnormal conditions.[2]

METHOD OF PROCEDURE

The morning after a night's fast, the contents of the stomach were aspirated. The subjects were then given one of two test meals. At first a shredded wheat biscuit and 400 cc. of tap water containing 6 mg. of phenolsulphonphthalein were used, but owing to the fact that such a test meal was

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* From the department of internal medicine, Washington University School of Medicine.

* This investigation was made possible by the financial assistance of Mr. and Mrs. J. Herndon Smith.

* Read in part before the American Gastro-Enterological Association, Atlantic City, N. J., May 3, 1926.

1. Baird, M. M., and Campbell, J. M. H.: The Importance of Estimating Chlorides in the Fractional Test Meal Samples, and Some Experiments with the Duodenal Tube, Guy's Hosp. Rep. **74**:40, 1924. Bolton, Charles, and Goodheart, G. W.: Duodenal Regurgitation Into the Stomach During Gastric Digestion, Lancet **1**:420, 1922.

2. We report results only from a representative number of the many subjects studied. Specimens containing excessive amounts of mucous or bile are not included. Patients with gastric carcinoma are also excluded, due to the frequent presence of blood in the gastric contents.

found to contain variable amounts of chlorides, a second test meal consisting of 400 cc. of distilled water containing 6 mg. of phenolsulphonphthalein was employed. At a definite period (45 minutes) after the test meal, the stomach was emptied as completely as possible. In certain cases on successive days, after removal of the contents of the stomach during fasting, test meals were given and the contents of the stomach removed at 30, 60, 90 and 120 minutes, respectively, after the test meal.

A comparative study was made of the free hydrochloric acid, total acidity and total chlorides of the contents during fasting and a similar study of the phenolsulphonphthalein concentration, the free hydrochloric acid, total acidity and total chlorides in a sample of the mixed chyme after the test meal. The presence of excess mucus and the presence or absence of bile were recorded. The free acid and total acidity were estimated according to the Toepfer method. The chlorides were determined by the direct Volhard procedure. To make comparison easy the chlorides reckoned as sodium chloride are expressed as tenth-normal hydrochloride acid.[3]

The factor of "test meal dilution"[4] was estimated in the following manner: 2 cc. of a filtrate of the sample was placed in the cup of a Hellige colorimeter and made alkaline by the addition of 2 or 3 drops of 40 per cent sodium hydroxide. The color was then compared against an alkalinized standard solution of phenolsulphonphthalein of the original concentration taken with the test meal.

In 1923, one of us (Gorham[4]) described a procedure for estimating the dilution of the gastric juice by the fluid taken with the test meal and for determining the fluid motility of the stomach. The principal of this is as follows: little, if any, water is absorbed in the stomach. This is also apparently true of certain dyes, such as phenolsulphonphthalein. If this is a fact and a fixed quantity of water (400 cc.) containing a definite amount of phenolsulphonphthalein (6 mg) is given as part of the test meal, the percentage of dye concentration in a sample of the contents of the stomach at a given period after ingestion of the test meal may be interpreted to approximate the dilution of the gastric juice by the fluid taken with the test meal. The total amount of dye solution remaining in the stomach at a given time after the meal is an index to the fluid motility of the particular stomach under given conditions.[5]

By "corrected acidity" and "corrected total chlorides" are meant the acid and chloride concentration in a sample of gastric contents after removal of the factor of test meal dilution.

Example.—If the dye concentration in the sample of gastric contents is 50 per cent of the dye concentration of the fluid taken with the test meal, it is obvious that in 100 cc of gastric contents, 50 cc. is water taken with the test meal, and only 50 cc. can be related directly to gastric secretion.

$$\frac{60 \text{ degrees (acidity as ordinarily obtained)} \times 100}{100\text{—}50 \text{ (per cent dilution)}} = 120 \text{ degrees}$$

3. One-tenth gram of sodium chloride is capable of producing approximately 17.1 cc. of tenth-normal hydrochloric acid or vice versa.

4. Gorham, F. D.: The Factor of Dilution in Gastric Analysis, J. A. M. A. **82**:1738 (Nov.) 1923.

5. This procedure is not to be confused with the method described in 1926 by Bloomfield and Keefer (Arch. Int. Med. **37**:819 [June] 1926). They also used a dye, but attempted to make a quantitative estimation of gastric secretion.

TABLE 1.—*Data of Normal Subjects*

	Phenol-sulphon-phthalein, per Cent	Free Hydro-chloric Acid	Total Acid	Total Chlorides	Corrected for Test Meal Dilution: Free Hydro-chloric Acid	Corrected for Test Meal Dilution: Total Acid	Corrected for Test Meal Dilution: Total Chlorides	Bile
Case 1 (M. M. H.)								
Contents during fasting	..	0	24	91	..	..	..	Negative
30 minutes	78	5	7	24	23	32	93	1 plus
60 minutes	40	9	11	55	15	18	91	1 plus
90 minutes	10	37	50	94	40	56	104	Trace
120 minutes	0	40	50	90	40	50	90	Negative
150 minutes	0	33	44	94	33	44	94	Negative
Case 2 (C. M. S.)								
Contents during fasting	..	0	12	89	..	..	..	Negative
30 minutes	52	24	32	51	50	66	106	Trace
60 minutes	30	28	38	72	40	54	102.5	1 plus
90 minutes	10	30	40	85	33	44	94	Negative
120 minutes	0	29	38	102	29	38	102	Negative
Case 3 (A. S.)								
Contents during fasting	..	18	34	124.3	..	..	..	Negative
30 minutes	75	20	26	33	80	92	133	Trace
60 minutes	21	54	65	85.5	62	80	107	1 plus
90 minutes	0	60	73	107	60	73	107	2 plus

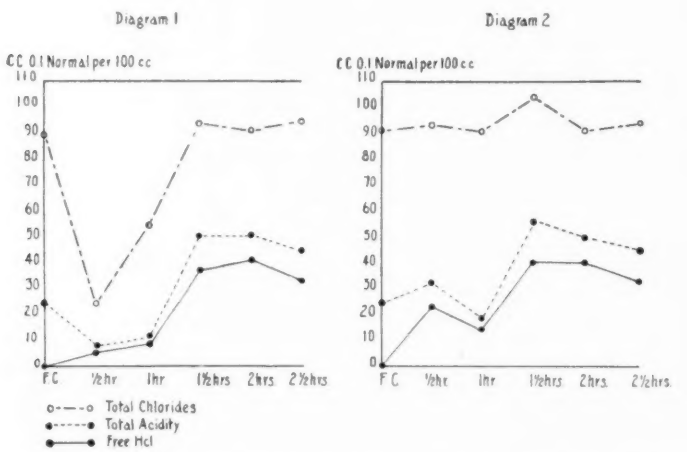

Chart 1.—Graphic illustration of case 1, table 1. Compare diagrams 1 (uncorrected) and 2 (corrected for test meal dilution). The degree of free hydrochloric acid, total acidity and total chlorides of the contents of the stomach during fasting are shown. The degrees of free hydrochloric acid, the total acidity and total chlorides at different digestive periods after a test meal consisting of 400 cc. of distilled water and 6 mg. of phenolsulphonphthalein are shown. Note the influence of test meal dilution on the so-called acidity curve as obtained by the fractional gastric analysis. In diagram 2, note the concentration level of the total chlorides of the fasting stomach contents and of the gastric chyme at different digestive periods after the test meal. Compare the chloride level with the acidity.

and if 60 degrees is the total acidity of the diluted sample as ordinarily obtained, then the "corrected total acidity" would be 120 degrees, which more nearly represents the acidity of the undiluted gastric juice.

RESULTS OF EXPERIMENTS

From a study of table 1 and charts 1, 2 and 3, a comparison may be made of the chloride concentration, the acidity and their relationship to one another in the contents of the stomach during fasting and in the gastric chyme at different digestive periods after the test meal. A comparison of diagrams 1 and 2 in charts 1, 2 and 3 illustrates diagramatically the influence of the factors of test meal dilution and gastric motility on the character of the so-called "acid secretion curve," as obtained by the fractional method of gastric analysis. It is noted in

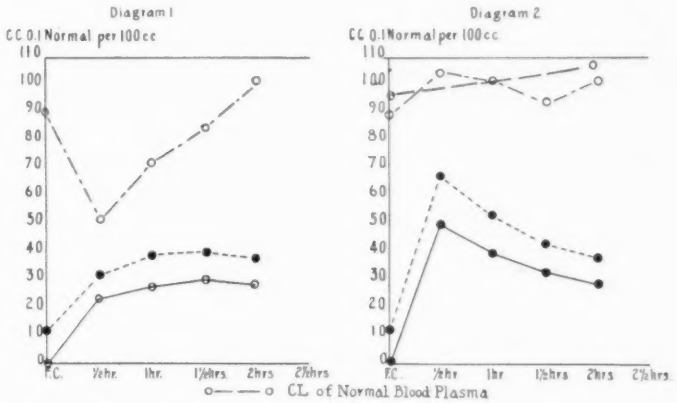

Chart 2.—Graphic illustration of case 2, table 1. Compare diagrams 1 (uncorrected) and 2 (corrected for test meal dilution). The degrees of free hydrochloric acid, total acidity and total chlorides of the contents of the stomach during fasting are shown. The degrees of free hydrochloric acid, total acidity and total chlorides at different digestive periods after a test meal consisting of 400 cc. of distilled water and 6 mg. of phenolsulphonphthalein are shown. Note the influence of test meal dilution on the so-called acidity curve as obtained by the fractional gastric analysis. In diagram 2, note the concentration level of the total chlorides of the contents of the stomach during fasting and of the gastric chyme at different digestive periods after the test meal. In diagram 2, compare the chloride level of the gastric contents with the chloride concentration of normal blood plasma (approximately 100 degrees).

these subjects that the chloride concentration of the contents of the stomach during fasting and of the gastric chyme after correction for test meal dilution approaches a similar level. A definite relationship does not exist between the acidity and total chloride concentration, the chlorides showing less fluctuation than the acidity.

In a subject in whom gastro-enterostomy had been successfully performed (table 2 and chart 4), a liquid test meal, as evidenced by the disappearance of the dye in the sample, left the stomach within thirty minutes after ingestion, denoting a relative fluid hypermotility. In this and similar subjects was found a marked variation between the free hydrochloric acid and the chloride levels.

TABLE 2.—*Data of Patient (C. D.) in Whom Gastro-Enterostomy for Ulcer Was Performed*

					Corrected for Test Meal Dilution			
	Phenol-sulphon-phthalein, per Cent	Free Hydro-chloric Acid	Total Acid	Total Chlorides	Free Hydro-chloric Acid	Total Acid	Total Chlorides	Bile
Contents during fasting	..	18	32	106				
30 minutes	20	23	27	87	29	33.5	111	1 plus
60 minutes	0	22	34	111	22	34	111	1 plus
90 minutes	0	21	26	109	21	26	109	2 plus
120 minutes	0	31	34	106	31	34	106	2 plus

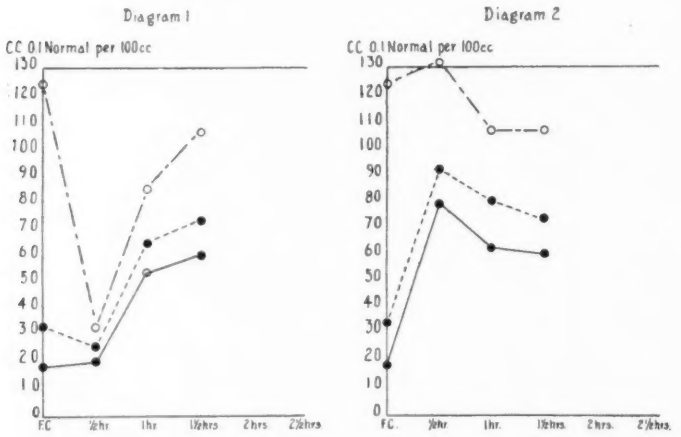

Chart 3.—Graphic illustration of case 3, table 1. Compare diagrams 1 (uncorrected) and 2 (corrected for test meal dilution). The degrees of free hydrochloric acid, total acidity and total chlorides of the contents of the stomach during fasting are shown. The degrees of free hydrochloric acid, total acidity and total chlorides at different digestive periods after a test meal consisting of 400 cc. of distilled water and 6 mg. of phenolsulphonphthalein are shown. Note the influence of the test meal dilution on the so-called acidity curve as obtained by the fractional gastric analysis. In diagram 2 note the concentration level of the total chlorides of the contents of the stomach during fasting and of the gastric chyme at different digestive periods after the test meal. Compare the chloride level with the acidity.

TABLE 3.—*Data of Patient (Mrs. N.) with Achylia Gastrica*

					Corrected			
	Phenol-sulphon-phthalein, per Cent	Free Hydro-chloric Acid	Total Acid	Total Chlorides	Free Hydro-chloric Acid	Total Acid	Total Chlorides	Bile
Contents during fasting	..	0	2	62	0	2	62	Negative
30 minutes	70	0	4	24	0	13	78	Negative
60 minutes	40	0	10	35	0	17	57	Negative
90 minutes	20	0	8	62	0	12	77	Negative
120 minutes	0	0	8	67	0	10	68	Negative

TABLE 4.—*Protocols of Normal Medical Students*

	Fasting			Test Meal			
Subject	Free Hydro-chloric Acid	Total Acid	Total Chlorides	Phenol-sulphon-phthalein, per Cent	Corrected Free Hydro-chloric Acid	Corrected Total Acid	Corrected Total Chlorides
B.	3	17	88.1	45	21.6	34.3	88.9
C. O.	4	13	76.35	30	25	33.5	69.1
E. S.	7	11.5	70.5	32	26	35.5	74.5
L. H.	10.5	21	99.8	30	13.5	20	91.3
P. R.	8	13.5	84.6	40	35.3	43.5	79.6
H. K.	Negative	11.3	99.1	35	13.4	25.1	100.5
W.	3	8	106.35	30	19.5	26	102.2
L. W.	8.5	14.3	89.3	40	27.5	43.3	84.1
H. A.	3	14.7	105.6	25	16.7	24.1	100.8
L. E.	0	18.1	87.31	30	6	19.5	84.1
D.	16.5	27	101.3.	40	32	41	109.3
S.	Negative	12.5	113.1	35	13	26.5	112.6
S. H.	6	14.5	113.4	30	32.1	43.4	111.5
S.	Negative	6	95.5	40	13.5	23	99.5
S. A.	0	10	79.3	43	11	18.5	81.2
G. M.	6	13.5	81.4	20	12.1	19.3	86.2
H. M.	17	26.5	98.7	25	24.5	33.1	99.1
F. W.	21.4	29.5	101.6	35	36	43	110.1
H. T.	16.1	24.3	87.1	26	22	29.1	92.15
P. R.	0	12	89.1	23	17.1	24.6	84.5
J. C.	9.1	16.3	84.1	20	19.1	23.1	91.3
C. C.	8.1	17.4	99.3	22	16	24	97.6
G. L.	17.9	28.4	93.1	40	24	36	99.15
Average	7.2	16.5	92.95	27.6	16.4	30.1	89.91

TABLE 5.—*Protocols of Patients with Duodenal Ulcer*

	Fasting			Test Meal			
Subject	Free Hydro-chloric Acid	Total Acid	Total Chlorides	Phenol-sulphon-phthalein, per Cent	Corrected Free Hydro-chloric Acid	Corrected Total Acid	Corrected Total Chlorides
R. M.	45	56	136.5	30	48	53	119.3
E. A. H.	28	30	119.7	9	35	40	109.4
J. C. P.	36	42	136.1	30	40	55	132.8
F. A. C.	2	5	133.6	10	34	50	138.4
W. H.	28	36	95.5	10	50	61	102.7
A. M. L.	40	42	129.4	18	52	60	135.8
W. H. R.	30.4	40	102.3	25	18	29	106.8
R. H. B.	36	42	112.6	30	38	44	119.7
C. K. C.	18	30	102.6	18	20	38	119.7
L. H. P.	15	21	106.7	10	20	30	111.7
J. A. H.	25	32	119.6	9	38	40	123.1
H. S.	29	33	100.8	15	44.7	54.1	98.7
W. W.	70.5	85	130.4	15	85.8	96	129.9
D. E.	32	48	116.3	20	51.2	62.5	127.2
W. C. B.	68	72	136.6	10	90	106	149.6
E. C. R.	60	68	136.8	42	70	75	139.4
G. W. S.	31	34	119.7	30	9.3	17	122.6
A. D.	6	14	112.7	15	61	80	114.9
M. C.	37	48	119.9	52	41.6	54	125.3
Average	33.5	40.9	119.3	20.9	44.5	54.9	122.4

TABLE 6.—*Protocols of Patients with Disease of the Biliary Tract*

Subject	Fasting			Test Meal			
	Free Hydrochloric Acid	Total Acid	Total Chlorides	Phenolsulphonphthalein, per Cent	Corrected Free Hydrochloric Acid	Corrected Total Acid	Corrected Total Chlorides
M. F.	0	6	102.6	22	11	19	111.2
J. C. B.	16	22	136.8	28	40	60	139.7
A. F. H.	28	37	120.7	25	42	58	137.8
J. D.	0	5	93.2	19	0	12	95.5
L. M. G.	0	6	101.2	8	8	16	95.5
W. T. T.	15	30	116.4	20	2	6	119.1
S. F.	6	8	119.7	40	26	38	133.7
A. A. R.	0	2	122.4	38	42	50	137.5
C. A. T.	19	22	98.7	10	32	40	104.8
P. B.	68	71	136.6	17	53	70	128.2
C. A. J.	19	22	87.2	20	40	50	110.5
J. R.	0	6	119.7	20	20	28.7	121.2
J. A.	0	16	119.5	15	18.2	28	128
E. W.		No fasting		10	38	46.6	90
J. G.	21	41	116	7	11.6	26.2	106
M. R.	5.5	7.6	81.1	22	13	19.6	78.2
I. G.	8	16	96.4	12	10.2	12.5	101.4
Average	12.8	19.8	104.2	19.5	23.9	34.2	114.1

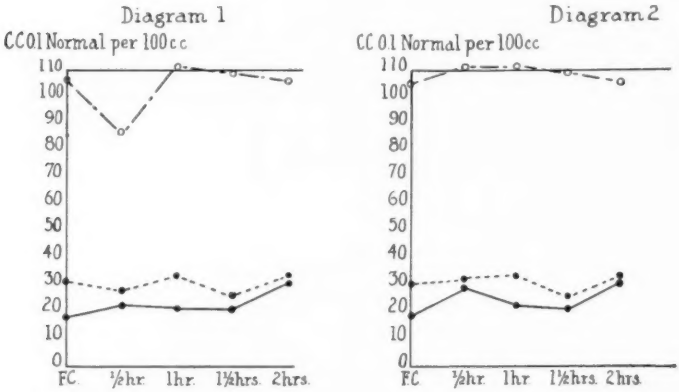

Chart 4.—Graphic illustration of table 2. Compare diagrams 1 (uncorrected) and 2 (corrected for test meal dilution). The degrees of free hydrochloric acid, total acidity and total chlorides of the contents of the stomach during fasting are shown. The degrees of free hydrochloric acid, total acidity and total chlorides at different digestive periods after after a test meal consisting of 400 cc. of distilled water and 6 mg. of phenolsulphonphthalein are shown. Note the influence of test meal dilution on the so-called acidity curve as obtained by the fractional gastric analysis. In diagram 2, note the concentration level of the total chlorides of the fasting stomach contents and of the gastric chyme at different digestive periods after the test meal. In diagram 2 (corrected), note particularly the relationship of the total chloride concentration level and acidity.

In certain pathologic states (table 3, chart 5 and table 7) such as are found in subjects with achylia gastrica (pernicious anemia), the average chloride concentration, as compared with that of normal persons (tables 1 and 4), was lower. In duodenal ulcer, disease of the biliary tract and benign pyloric obstruction (tables 5, 6 and 8), there was found a higher level as compared to normal, but no higher than found in a group of miscellaneous cases.

TABLE 7.—*Protocols of Patients with Achylia Gastrica*

	Fasting			Test Meal			
Subject	Free Hydrochloric Acid	Total Acid	Total Chlorides	Phenolsulphonphthalein, per Cent	Corrected Free Hydrochloric Acid	Corrected Total Acid	Corrected Total Chlorides
M.	0	3	44	10	0	7	49.5
T. R.	0	8	47.4	15	0	9.5	53.2
W.	0	5	47	20	0	8.3	49.1
E. W.	0	5	63.1	18	0	7.4	58.4
S.	0	7.9	49.1	15	0	15	52.1
J. W.	0	8	68.1	20	0	11	66.4
H. P.	0	6.5	63.1	15	0	9.5	56.1
L. O.	0	8.7	88.2	20	0	11.2	84.2
T. R.	0	10.5	62.5	Trace	0	12	47.4
Mrs. N.	0	9.5	68.4	10	0	11.2	64.1
N. I.	0	6.8	61.2	9	0	10.3	57.2
Average	0	7.8	60.1	12.4	0	10.2	57.9

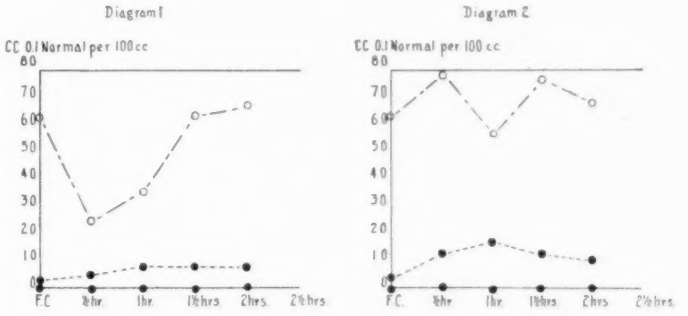

Chart 5.—Graphic illustration of table 3. Compare diagrams 1 (uncorrected) and 2 (corrected for test meal dilution). The degrees of free hydrochloric acid, total acidity and total chlorides of the contents of the stomach during fasting are shown. The degrees of free hydrochloric acid, total acidity and total chlorides at different digestive periods after a test meal consisting of 400 cc. of distilled water and 6 mg. of phenolsulphonphthalein are shown. Note the influence of test meal dilution on the so-called acidity curve as obtained by the fractional gastric analysis. In diagram 2, note the concentration level of the total chlorides of the fasting stomach contents and of the gastric chyme at different digestive periods after the test meal. In diagram 2 (corrected for test meal dilution) note particularly the relationship of the total chloride concentration level, free (achlorhydria) and total acidity.

TABLE 8.—*Protocols of Miscellaneous Group of Patients Test Meal*

	Corrected Free Hydrochloric Acid	Corrected Total Acidity	Corrected Total Chlorides		Corrected Free Hydrochloric Acid	Corrected Total Acidity	Corrected Total Chlorides
Hypoacidity...	14.5	21.8	71.8	Chronic appendicitis.....	58	67	163.2
Hypoacidity...	10	15	147.9	Chronic appendicitis.....	68	77	194.2
Hypoacidity...	20	36	187	Chronic appendicitis.....	22	34	87.5
Hypoacidity...	8.5	30	144.5	Chronic appendicitis.....	86	102	157
Hypoacidity...	9.3	17	132.6	Chronic appendicitis.....	38	54	151.2
Hypoacidity...	11.6	26.6	106	Migraine.....	42	53	123.12
Hyperacidity..	70	77	146.2	Colitis.....	45	63	147.9
Hyperacidity..	70	90	121.3	Colitis.....	54	66.4	102
Hyperacidity..	82	112.4	122.6	Simple goiter.....	36	62	149.6
Hyperacidity..	88	102	154.7	Gastro-enterostomy.....	28	52	144
Hyperacidity..	90	106	149.6	Gastro-enterostomy.....	40	60	130.9
Hyperacidity..	68	90	136	Gastro-enterostomy.....	108	158	186.7
Simple anemia.	41	88	110.4	Gastro-enterostomy.....	42	53	146.8
Simple anemia.	36	64	153.9	Gallstones.....	24	42	174
Simple anemia.	10	15	144.9	Neurosis.....	38	44	136.8
Benign pyloric obstruction..	75	103	204	Neurosis.....	20	36	187
Benign pyloric obstruction..	71	85	170	Chronic myocarditis.....	35	46	122
Benign pyloric obstruction..	45	59	144	Chronic pyelitis.....	66	78	153
Constipation..	51	75	187	Postoperative adhesions	53	67	154.3

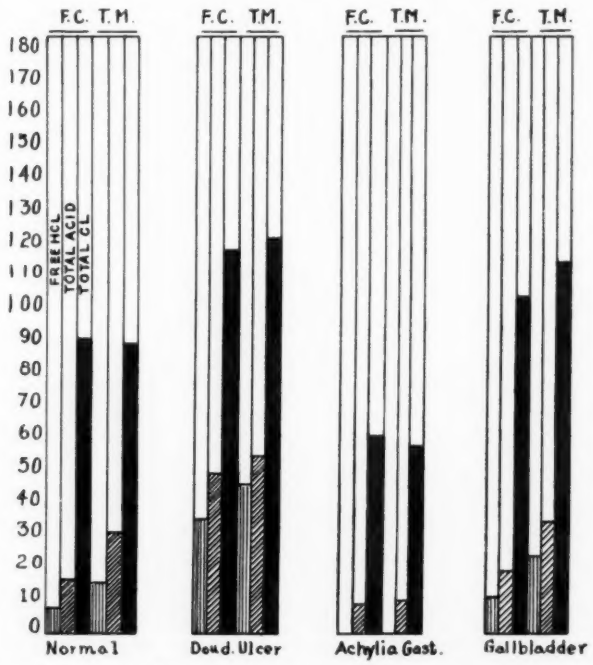

Chart 6.—Graphic illustration of tables 4, 5, 6 and 7. Compare degrees of free hydrochloric acid, total acidity and total chlorides of the contents of the stomach during fasting and of the gastric chyme after correction for test meal dilution. Aspiration of contents forty-five minutes after test meal.

Tables 4, 5, 6, 7 and 8 and chart 6 illustrate the results obtained by the use of the single aspiration procedure. From these tables, it is possible to make a comparative study of data obtained from subjects representing both normal and pathologic conditions.

COMMENT

From our observations, we agree with Bolton and Goodheart that the absence of free hydrochloric acid or the presence of a low active hydrochloric acid concentration in the contents of the stomach is not necessarily an indication that gastric secretion is correspondingly diminished, and that in persons with achlorhydria the total chlorides of the contents of the stomach may be of normal concentration. We can hardly agree, however, with the assumption that when the total chlorides are at a normal level it may be assumed that a low acidity is necessarily due to excessive neutralization.

Baird and Campbell stated that diminished gastric secretion can be distinguished from normal secretion with excessive neutralization by a comparative study of the total chloride concentration and acidity of the stomach contents. We do not concur in this opinion, as it cannot be assumed that the chlorides of the contents of the stomach are necessarily a volumetric index to the production of hydrochloric acid by the gastric glands. From a study of the subjects with achylia gastrica (table 7), it is obvious that in some instances a chloride concentration approaching the normal level was encountered. During investigation it was found that the chloride concentration of the duodenal contents obtained by means of the duodenal tube and bile taken from the common duct and the gallbladder at operation was as high or higher than that of the contents of the stomach; therefore, the regurgitation of the intestinal fluids into the stomach is in some instances an important factor in determining the height of the chloride level in the gastric contents.

It was noted that the total chloride concentration of the fasting contents and of the gastric chyme, at different digestive periods after correction for dilution, frequently approached similar levels. In the normal subjects a similarity was noted between the chloride level of the contents of the stomach and that found in normal blood plasma. It is noted from a comparative study in subjects showing hypoacidity and hyperacidity (table 8) that the chloride level may be similar in the two conditions.

In relation to this investigation, we would call attention to the work of Gamble and McIver [6] who estimated the total chlorides and total bases of gastric juice obtained from pouches made in the fundic and

6. Gamble, J. L., and McIver, M. A.: Fixed Base in Gastric Juice, J. Exper. Biol. & Med. **23**:439 (March) 1926.

pyloric region of the stomach in animals. They observed that during different phases of digestion the chlorides were nearly stationary, while there was a wide range in the variation of the total bases.[7]

SUMMARY

1. In the subjects without symptoms of disease, the total chloride concentration of the contents of the stomach during fasting and of the gastric chyme after correction for test meal dilution frequently approached the same level; in many instances this concentration showed a similarity to that of normal blood plasma.

2. The chloride concentration of the contents of the stomach during fasting and of the gastric chyme was variable in different pathologic conditions, a fairly constant increase being found in pyloric obstruction, duodenal ulcer and disease of the biliary tract. In achylia gastrica, the total chloride concentration was usually low but in some instances approached the average level found in normal persons.

3. The relationship of the acidity and total chlorides of the contents of the stomach during fasting and of the gastric chyme after the standard test meal was exceedingly variable in both health and disease. The acidity showed a greater fluctuation than the chloride concentration, this being especially noteworthy in subjects showing hypoacidity, hyperacidity and those in whom gastro-enterostomy had been successfully performed.

4. From our experimental study, especially in subjects showing achylia gastrica, it would appear that the chloride concentration of the contents of the stomach as determined by the direct Volhard method is not necessarily a volumetric index to the production of hydrochloric acid by the gastric glands.

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7. We take this opportunity to acknowledge the assistance given us in this investigation by Dr. Ethel Ronzoni, of the Department of Internal Medicine.

GASTRIC SECRETION

ITS ALTERATION BY THE USE OF ATROPINE, EPINEPHRINE AND PILOCARPINE

A. M. ALTSHULER, M.D.
DETROIT

Pharmacologic substances which act on the sympathetic and parasympathetic nervous system, particularly those which act on the nerve supply of the gastro-intestinal tract, have been investigated extensively. The explanation for this lies in the various therapeutic applications to which such knowledge could be directed, as well as in the fact that numerous conflicting reports of results of similar experiments have led to the desire to arrive at the truth by further study. A brief résumé of the more important investigations which have been carried out with atropine, epinephrine and pilocarpine will aid materially in interpreting the results of this study. A review of the work of other investigators reveals plainly the conflicting conclusions drawn from these experiments.

ATROPINE

In 1882, Netchaev,[1] working in Pavlov's laboratory, found that atropine paralyzes gastric secretion. This work was later confirmed by Ushakov [2] who showed that atropine paralyzed the gastric secretion in animals during the first (cephalic) stage of secretion whether initiated by sham feeding or by stimulation of the vagus nerve by means of an induction current. Sanotzki [3] showed that in the second stage (gastric phase) of gastric secretion, atropine diminished the secretion, provided the stimulant to secretion was in the stomach itself or in the isolated pylorus. If, however, the chemical stimulants to secretion were introduced hypodermically or intravenously, then atropine did not affect it.[4] Riegel [5] found a diminished gastric secretion with the

1. Netchaev, A. A.: On the Inhibitory Action of Atropine, Morphine and Chloral Hydrate upon the Gastric Secretion and the Stimulation of the Sensitive Nerves, Diss., St. Petersburg, 1882.

2. Ushakov, V. G.: On the Action of the Nerve Vagus upon the Gastric Secretions in a Dog, Diss., St. Petersburg, 1896, p. 20.

3. Sanotzki, A. S.: The Stimulation of the Gastric Secretions, Diss., St. Petersburg, 1892, p. 80.

4. Zeliony, G. P., and Savitch, V. V.: On the Mechanism of the Gastric Secretion, Tr. Obstsche. Russk. Vrach. **79**:1, 1911-1912; Zur Physiologie des Pylorus., Arch. f. d. ges. Physiol. **150**:128, 1913.

5. Riegel, A.: Ueber Medicamentose Beeinflussung der Magensecretion, Ztschr. f. klin. med. **37**:381, 1899.

use of atropine, while Bylina [6] found that it diminished gastric secretion only in cases of hypersecretion. Auer and Meltzer [7] stated that atropine causes paralysis of the vagus endings connected with Auerbach's plexus, with a resultant diminution of secretion. Gerhard Katsch [8] has shown that small doses of atropine stimulate Auerbach's plexus and at the same time paralyze the nerve endings of the vagus with a resultant decrease in peristalsis. Lasch [9] found that injections of atropine had two separate and opposite actions; first, an increase in peristalsis which lasted only a few minutes, and second, following this increase, a prolonged stage of inhibition of peristalsis which ended in complete atony. He explained this apparent paradox by stating that atropine first produces a transitory stimulation of the parasympathetic system, and later paralysis of the parasympathetics. Zung and Tysebaert,[10] working with dogs, observed diminished contractions of the stomach after injections of atropine. Small doses did not have any effect on the contractions, but they did result in lessened tonus. Klee [11] observed in animals, and Otvös [12] observed in man, increase in pylorospasm and a delayed emptying of the stomach following injections of atropine. Stranz [13] confirmed Otvös' observations on the prolongation of the evacuation time. Hecht,[14] experimenting with the isolated stomach of rats, found that the action of atropine was variable. He explained this variability by the presence or absence of peristalsis inducing substances, and of choline in particular. Kalk and Siebert [15] did not find any changes in the hydrochloric acid concentra-

6. Bylina, A.: On the Analysis of the Disturbance of Gastric Secretion, Russk. Vrach. **12**:83, 1913.

7. Auer, J., and Meltzer, S. J.: Action of Ergot upon the Stomach and Intestines, Am. J. Physiol. **17**:143, 1906.

8. Katsch, Gerhard: Beiträge zum Studium der Darmbewegungen: 3. Pharmakologische Einflusse auf den Darm (bei physiologischen Versuchsanordnung), Ztschr. f. exper. Path. u. Therap. **12**:253, 1912-1913.

9. Lasch, C. H.: Röntgenologische Untersuchungen über den Einfluss des Atropins auf die Magenmotilität, Klin. Wchnschr. **17**:840, 1922.

10. Zung, E., and Tysebaert, J.: Action of Atropine Sulphate on Isolated Stomach and Intestines, J. Pharm. and Exper. Therap. **8**:325, 1916.

11. Klee, P.: Beiträge zur pathologischen Physiologie der Mageninnervation: 2. Pylorus Insuffizienz and praepylorischer Gastrospasmus, Deutsches Arch. f. klin. Med. **133**:265, 1920.

12. Otvös, E.: Beiträge zur pharmakologischen Beeinflüssbarkeit der Magenmotilität, Klin. Wchnschr. **4**:445, 1925.

13. Stranz, J.: Untersunchungen über die diagnostische Brauchbarkeit der Atropinprobe des Magens, Med. Klin. **2**:59, 1926.

14. Hecht, P.: Untersunchungen über die Wirkung des Atropin auf den überlebenden Magen, Deutsches Arch. f. klin. Med. **136**:296, 1921.

15. Kalk, H., and Siebert, P.: Untersuchung über die Wirkung von Atropin und Belladonna (Bellafolin) auf die Magenfunktion, Arch. f. Verdauungskr. **40**: 313, 1927.

tion after atropine had been given. They also confirmed the observations of Katsch and Kalk [16] that the acidity of the gastric juice is not influenced by atropine and that the evacuation time of the stomach is prolonged following an injection of atropine. They did not find any regular decrease in acidity with atropine, the majority of their determinations, in fact, showed an increase. Keeton, Luckhardt and Koch,[17] on the contrary, experimenting on dogs with a Pavlov stomach, found that atropine inhibits the gastric secretion. They emphasized that from 50 to 80 per cent of the total gastric secretion was arrested before the hydrochloric acid dropped. Rehfuss [18] also found that large doses of atropine given hypodermically caused a decrease in psychic secretion and in the gastric acidity, but it never resulted in complete disappearance of the secretion. Pokras and Michelson,[19] applying the method of investigation of Bylina (in which the reflectoric stage of digestion was eliminated), found that atropine was a potent substance in diminishing hypersecretion. Crohn,[20] on the other hand, stated that 1/65 grain (0.00101 Gm.) of the drug given hypodermically one-half hour after eating did not affect the motility of the stomach, but raised the average of acidity from 32 acid per cent to 75; while Lockwood and Chamberlin [21] stated that atropine depresses both the secretory and motor activity of the stomach. Pongs [22] noted a diminished gastric secretion and a prolonged emptying time of the stomach after the administration of atropine, and his observations are confirmed by Rall.[23] Keefer and Bloomfield [24] found that the amount of gastric secretion was less after atropine had been administered than when it was not

16. Katsch, G., and Kalk, H.: Zum Ausbau der Kinetischen Methode für die Untersuchung des Magenchemismus. 3. Mitteilung die Chloride des Magensaftes besonders bei Salzsäuremangel, Klin. Wchnschr **5**:881, 1926.

17. Keeton, R. W.; Luckhardt, A. B., and Koch, F. C.: Gastrin Studies: 4. The Response of the Stomach to Food and Gastrin Bodies as Influenced by Atropine, Am. J. Physiol. **51**:469, 1920.

18. Rehfuss, M. E.: Action of Atropine on Gastric Secretion, Tr. Sect. Gastro-Enterol. & Proct., A. M. A. 25, 1918.

19. Pokras, S., and Michelson, V.: Vegetatives Nervensystem und Magensecretion, Arch. f. Verdauungen. **38**:373, 1926.

20. Crohn, B. B.: Studies in Fractional Estimation of Gastric Contents, Am. J. M. Sc. **155**:801, 1918.

21. Lockwood, B. C., and Chamberlin, H. G.: The Effect of Atropin on Gastric Function, Arch. Int. Med. **30**:806, 1922.

22. Pongs: Die Beeinflussung der Säureverhaltnisse des Magens durch Atropin, 33. Kongress d. Deutsch. ges. f. inner, med., 1921, p. 452.

23. Rall, T.: Ueber den Einfluss des Atropins auf die secretorische und motorische Function des gesunden Magens, Ztschr. f. d. ges. exper. Med. **52**:752, 1926.

24. Keefer, C. S., and Bloomfield, A. L.: Effect of Atropine on Gastric Function in Man, Arch. Int. Med. **38**:303, 1926.

given. They emphasized that the type of secretion was markedly altered by atropine. They pointed out that normally there is a great variation in the emptying time of the stomach as determined by their method, and these variations are also present after the administration of atropine.

EPINEPHRINE

The experiments with epinephrine in man as well as in animals also yields contradictory results. The action of epinephrine on the motor activity of the stomach results in a picture identical with the so-called "sympathetic stomach." Elliot [25] has shown in animals, that injections of epinephrine makes the stomach large, flaccid and weak in peristalsis. Katsch [26] observed the same thing in man, the entire stomach relaxing and the emptying of the stomach retarded following its use. Klee,[27] confirmed these observations in roentgen-ray study of cats. Bickel,[28] however, stated that there is a preliminary stage after the injection of epinephrine in which the tonus of the stomach is increased, the relaxation coming later in the second stage. Kolm and Pick [29] observed an "inverse" vagotropic action following the use of epinephrine. Yukawa,[30] G. Sirotinin,[31] and Loeper and Verpy [32] all found an increase in gastric secretion following injection of epinephrine. The latter two investigators found the hydrochloric acid increased. Opposed to this, is the observation of Hess and Gundlach [33] who found always an inhibition of secretion following the injection of epinephrine; and of Thomas [34] who found that epinephrine increases the tonus of the pyloric sphincter when the latter is relaxed and decreases the tonus when it is contracted. Badylkes [35] found that epinephrine increases the gastric

25. Elliot, T. R.: The Action of Adenalin, J. Physiol. **32**:401, 1905.

26. Katsch, G.: Der Menschliche Darm bei pharmakologischer Beeinflussung seiner Innervation, Fortschr. a. d. Geb. d. Röntgenstrahlen. **21**:159, 1914.

27. Klee, P.: Beitrage zur pathologischen Physiologie der Mageninnervation, D. Arch. f. klin. Med. **128**:204, 1919.

28. Bickel, A.: Der Nervöse Mechanismus der Secretion der Magendrüsen und der Muskelbewegungen am Magendarmkanal, Ergbn. d. Physiol. **24**:228, 1925.

29. Kolm, R., and Pick, E. P.: Ueber der Anderung der Adrenalinwirkung nach Erregung der Vagalen Endapparate, Arch. f. d. ges. Physiol. **184**:79, 1920.

30. Yukawa, G.: Klinisch-experimentelle Untersuchungen der Adrenalinwirkung auf die Magendrüsen, Arch. f. Verdauungskr. **14**:166, 1908.

31. Sirotinin, B.: Action of Adrenalin on the Secretion of a Heidenhain's Stomach of a Dog, Wratchebnoje Dielo **18**:24, 1923.

32. Loeper, M., and Verpy, G.: L'áction de l'ádrenalin sur le tractus digestif, Compt. rend. Soc. de biol. **53**:793, 1917.

33. Hess, W. R., and Gundlach, R.: Der Einfluss Adrenalins auf die Secretion des Magensaftes, Arch. f. d. ges. Physiol. **185**:122, 1920.

34. Thomas, J. E.: The Action of Adrenalin on Pyloric Sphincter, Proc. Soc. Exper. Biol. & Med. **23**:748, 1925-1926.

35. Badylkes, S. O.: Klinisch-physiologische Beobachtungen über den Einfluss einiger Hormone auf die Magensecretion (Experimentelle Untersuchung), Arch. f. Verdauungskr. **34**:105, 1924.

acidity in 80 per cent of his cases and decreased it in 20 per cent. Michelson and Neumark [36] stated that epinephrine increases gastric acidity in normal conditions, while in cases of hypersecretion the acidity is lowered. Dixon [37] noted contraction of the frog's stomach following an intravenous administration of epinephrine, while Cushny [38] noted inhibition of all gastric motility immediately after its injection. Petrovic [39] showed experimentally that epinephrine does not hinder the evacuation of water from the stomach. Gruber [40] thought that the varying actions of epinephrine on the stomach depends on its concentration—weak solutions producing increase in tonus, stronger solutions producing inhibition.

PILOCARPINE

Tshurilov [41] found that pilocarpine acted as a weak stimulant to the gastric glands. Doses of from 0.003 to 0.005 Gm. hypodermically, which were sufficient to produce profuse secretion of saliva and mucus from the nose and stomach, did not have any effect on the gastric glands. Large doses, however, cause relatively greater secretion of the salivary glands than of the stomach (Zitovitch).[42] Riegel [5] and Ehrmann [43] found an increase in the secretion of gastric juice following the administration of pilocarpine, but the acidity remained unchanged. Kljutcharev [44] reported its use in twelve cases in which he found a decrease in acidity following its administration in eight cases, unchanged acidity in one case, while in three cases, the acidity was raised. Kalk,[45] reported thirty cases, and stated that the acidity was diminished in the majority of them. Katsch and Egan [46] also found a decrease in

36. Michelson, V., and Neumark, I. E.: Atropin, Adrenalin, Pilocarpin, und ihre Wirkung auf die Magensecretion und ihre Phasen, Arch. f. Verdauungskr. **39**:275, 1926.

37. Dixon, E.: Effect of Adrenalin on Frog's Stomach, J. Physiol. **30**:97, 1903.

38. Cushny, A. R.: Pharmacology and Therapeutics, Philadelphia, 1918, p. 369.

39. Petrovic, A.: Ueber die Wirkung von Atropin und Adrenalin auf die Magenentlehrung beim Menschen, Deutsche. med. Wchnschr. **51**:1619, 1925.

40. Gruber, C. M.: The Effect of Epinephrine on Excised Strips of Frogs Digestive Tracts, J. Pharmacol. & Exper. Therap. **20**:321, 1922.

41. Tshurilov, I. A.: The Secretory Poisons in Regard to the Gastric Secretion, Diss., St. Petersburg, 1894.

42. Zitovitch, I. S.: The Action of Pilocarpin on the Secretion of the Gastric Glands, Tr. Obstschestva Russk. Vrach. **69**:324, 1902.

43. Ehrmann, R.: Physiologische und Klinische Untersuchungen über die Magensaftsecretion. Internationale Beitr. z. Path. u. Therap. der Ernährungsstörungen **3**:382, 1911-1912.

44. Kljutcharev, S.: On the Importance of Determining the Different Stages of Digestion in Accordance with the Clinical Observations, Terapevticheski Arch. **2**:3, 1924.

45. Kalk, G.: Ueber den Einfluss des Pilocarpinsauf die Tättigkeit des Menschlichen Magens, Arch. d. Verdauungskr. **32**:219, 1924.

46. Katsch, G.: Ueber Hyperacidität, Klin. Wchnschr. **18**:902, 1922.

acidity following the administration of pilocarpine. Bennett [47] reported conflicting results. Michelson and Neumark [36] explained the decrease in gastric acidity by the increase in secretion of mucus and the delayed emptying time of the stomach with resultant dilution.

The foregoing brief survey of the experimental work with atropine, epinephrine and pilocarpine reveals many discrepancies and much experimental data which seems conflicting or directly contradictory. If the observations are accurate, these discrepancies can be accounted for only by assuming that the various experiments were carried out on stomachs that were in different functional states when the experiments were begun. Zimnitzky [48] has shown that the action of drugs on functioning cells depends on what phase of activity those cells are in when the drug reaches them. Thus, a drug which would result in stimulation of the cell's activity if acting on a cell at rest, could result a little later in perhaps increased stimulation, or, if the cell were already maximally stimulated, might even result in inhibition by exhausting the cell through the overload. In other words, dependent on what phase of activity the cell were in, the same drug, acting on the same cell, might at one time result in stimulation, and at another time in inhibition. By bearing this in mind, it is possible to reconcile apparently contradictory observations in regard to these vagotropic and sympatheticotropic substances. It is reasonable to assume that disturbances of the gastric secretion may be dependent on two essentially different bases; i.e., it may be that the secreting cells are normal cells, but due to local or constitutional factors they are kept in such a phase of activity that when a normal stimulus, such as food, reaches them, they do not react as would a normal cell at rest, but react abnormally, either by hypersecretion or by inhibition with a decrease or absence of secretion; or, again, the cells may be pathologic cells, which even at rest do not respond to ordinary stimuli as would normal cells.

Other investigators [50] and I,[49] employing the method of Zimnitzky,[48] have demonstrated that, in general, there are characteristic types of secretion in various gastric and constitutional disturbances. There is also a characteristic normal type of secretion. As the same method was used in obtaining the results reported in this article, a brief

47. Bennett, Isod: The Modification of Gastric Function by Means of Drugs, Brit. M. J. **1**:366, 1923.

48. Zimnitzky, S. S.: Disturbance of the Secretory Function of the Glands of the Stomach, Moscow, 1926.

49. Altshuler, A. M.: A New Method of Gastric Analysis, Ann. Clin. Med. **5**:464, 1926.

50. Gurvitch, I. L.: On the Knowledge of the Function of the Gastric Cells Under the Influence of the Vagotrope and Sympaticotrope Substances, Trudy 7go s'ezda Therapevtov. **7**:280, 1925.

description of the technic and of the types of gastric secretion differentiated by this method follows. A more detailed report can be found in one of my previous articles.[19] The procedure is as follows: The patient is instructed to refrain from food or drink, starting at 6:00 p. m. of the day previously; at 8:00 a. m. a Rehfuss tube is introduced into the stomach. The contents of the fasting stomach are aspirated with the patient in various positions and the position of the tube is altered until all the contents are aspirated. The test breakfast of 200 cc. of plain warm beef broth (400 Gm. of lean beef in 1,000 cc. of water) is given the patient who is instructed to sip it for a period of five minutes. Fifteen minutes after the breakfast is started, 10 cc. of the contents of the stomach are aspirated. This is repeated every fifteen minutes for four times. Before each aspiration, the patient is requested to shake himself well. At the end of sixty minutes, the stomach is emptied; 200 cc. of the same meat broth is given, and the same procedure is repeated for another sixty minutes. The contents are examined at once. The types of gastric secretion determined by this method are classified as follows: (1) The normal type. The characteristic of the normal type is that the sum of acidity for the second hour is greater than that of the first hour (average usually being from 15 to 25 per cent). (2) Asthenic type. Here the total figures for the first hour are greater than for the second. This may be even with cases of hyperacidity. (3) Inert type. This type is characterized by the fact that at the beginning, the response of the stomach cells to the stimulus is sluggish, but after the stimulus of the first test breakfast, administration of the second test breakfast causes a sudden increase in gastric secretion. Therefore, the work of the second hour is quantitatively decidedly greater than the first (up to 50 per cent). (4) The isosecretory type. Here the total amount of work for the first and second hour is the same. (5) Torpid type. In this case, neither the first nor the second test breakfast produces enough stimulation of the gastric cells to reveal the presence of free hydrochloric acid. In these cases, one must distinguish between functional and organic torpor. In general, it can be shown that one of these types of gastric secretion tends to be characteristic in various local or constitutional disturbances.

In the present investigation, the type of secretion present was determined in each patient studied. After this had been done, allowing an interval of several days, the patient was given a subcutaneous injection of either atropine, epinephrine or pilocarpine together with the first test breakfast. Atropine was given in the form of 1/50 grain (0.00130 Gm.) of atropine sulphate; epinephrine was given in the form of solution of epinephrine hydrochloride, 1-1000 in a dose of 1 cc.; pilocarpine was given in the form of 1/4 grain (0.01620 Gm.) of pilocarpine

hydrochloride. A check on the action of the atropine was made by determining the dryness of the mouth, pharynx and larynx; by noting the changes in the pulse rate, dilatation of the pupil and dizziness. The action of the epinephrine was checked by noting the pulse rate, the blood pressure, paleness of the face, tremor, and by the result of the urinalysis. The physiologic activity of the pilocarpine was checked by noting the pulse rate, salivation, tearing, and nasal discharge, nausea and vomiting, diarrhea and flush of the face; and in all cases the subjective observations of the patient were determined.

The purpose of this study was to determine the effect, if any, of administering atropine, epinephrine and pilocarpine in altering the

TABLE 1.—*Acidity of Contents of Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	8	12	14	19
After 30 minutes	12	22	26	34
After 45 minutes	28	38	38	43
After 60 minutes	23	30	18	28
Total	71	102	96	124

TABLE 2.—*Acidity of Contents of Stomach After Ingestion of Atropine Sulphate*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	12	19	6	12
After 30 minutes	25	28	18	25
After 45 minutes	28	40	18	32
After 60 minutes	24	28	12	19
Total	89	115	54	88

normal type of secretion in normal persons, and of their effect in altering the various abnormal types of secretion thought to be characteristic of certain gastro-intestinal and constitutional disturbances. Characteristic protocols in each group follow:

REPORT OF CASES

CASE 1.—A. H., a man, aged 44, had never had any gastro-intestinal complaints. The results of a general physical examination showed him to be normal. Urine analysis and stool examination were normal. Twelve cubic centimeters of the contents of the stomach was aspirated while the patient was fasting; the free hydrochloric acid was found to be 6 to acid phenolphthalein and the acidity was found to be 18 to acid phenolphthalein.

This same patient was given 1/50 grain (0.00130 Gm.) of atropine sulphate hypodermically at the time of the first test breakfast, when

the following determination was made a few days later. The results are shown in table 2.

A few days later, the same patient was given ¼ grain (0.01620 Gm.) pilocarpine hydrochloride hypodermically at the time of his first test breakfast. The results of the gastric analysis are shown in table 3.

After an interval of a few days, the patient was given 1 cc. of solution of epinephrine hydrochloride (1:1000) subcutaneously together with his first test breakfast. The results of gastric analysis are shown in table 4.

TABLE 3.—*Acidity of Contents of Stomach After Ingestion of Pilocarpine Hydrochloride Hypodermically*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	6	18	25
After 30 minutes	0	8	35	38
After 45 minutes	14	26	42	56
After 60 minutes	26	28	36	43
Total	40	68	131	162

TABLE 4.—*Acidity of Contents of Stomach After Ingestion of Epinephrine Chloride Subcutaneously*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	28	36	6	14
After 30 minutes	32	39	32	43
After 45 minutes	42	54	23	34
After 60 minutes	34	44	15	21
Total	136	173	76	112

If the normal type of gastric secretion is compared with the gastric secretion in this type following the administration of atropine it is noted that following the stimulation by atropine, the secreting cells respond rapidly during the first hour, but soon become exhausted during the second hour; that is to say, under the influence of atropine, the normal type of secretion is converted into the asthenic type.

After pilocarpine is given there is a sluggish secretion during the first hour, while during the second hour there is a gradual increase. Thus, pilocarpine converts the normal type of gastric secretion into the inert type. This observation may possibly account for the contradictory reports on the effect of pilocarpine on gastric secretion made by various investigators. Those who watched the first phase of the action of pilocarpine would report either inhibition of secretion or no alteration

of secretion, while those who observed the second phase of the gastric secretion for a longer period of time, would find an increase in secretion.

After the administration of epinephrine, the gastric cells respond with an increased secretion during the first hour, while in the second hour, the secretion is sluggish. In other words, epinephrine converts the normal type of gastric secretion into the asthenic type.

The foregoing observations are in accord with those of Zimnitzky,[48] Gurvitch,[50] and Pshenitchnikov,[51] who found that atropine and epinephrine converted the normal type of secretion into the asthenic type, while pilocarpine changed it into the inert type.

Similar studies were carried out with patients who demonstrated abnormal types of gastric secretion.

CASE 2.—I. R., a married woman, complained of gas, pressure in epigastrium, eructation, headaches localized in temples "like strokes of a hammer," and globus hystericus. This patient had a good appetite. The results of the

TABLE 5.—*Acidity of Contents of Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	8	0	7
After 30 minutes	0	6	0	9
After 45 minutes	0	12	0	10
After 60 minutes	0	8	0	10
Total	0	34	0	36

examination of the stool and urine were normal. No abnormality was noted on physical examination. Diagnosis of hysteria was made. The results of gastric analysis are shown in table 5. Twenty-four cubic centimeters of the contents of the stomach was aspirated while the patient was fasting; Guaiac was found to be negative, the free hydrochloric acid 4, and the total acidity 12.

It would be desirable, in this case, to have a method to determine with some degree of assurance whether this torpor belonged to the functional or to the organic group. With this in mind, the foregoing procedure was repeated a few days later, but at this time, 1 cc. of epinephrine was given subcutaneously at the time of the first test breakfast. The results are shown in table 6.

By the use of epinephrine, the torpor was found to be a functional one, since the epinephrine converted the type of gastric secretion from one of torpor to the asthenic type. The gastric cells were still capable of responding with secretion, although they had been kept in such a

51. Pshenitchnikov, cited by Zimnitzky, S.: Ueber die neue Methode der functionellen Magenuntersuchungen und ihre Resultate, Ztschr. f. d. ges. Exper. Med. **44**:181, 1924.

phase of activity that a normal stimulus was not any longer capable of stimulating them.

In contrast with the foregoing case, is the following one in which the condition is diagnosed as carcinoma of the stomach.

CASE 3.—J. H., a man, aged 51, an iron molder, had been complaining of pain in the epigastrium, lack of appetite and loss of weight during the past

TABLE 6.—*Acidity of Contents of Stomach After Ingestion of Epinephrine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	12	28	9	19
After 30 minutes	21	39	18	25
After 45 minutes	28	42	23	38
After 60 minutes	19	23	12	30
Total	80	132	62	110

TABLE 7.—*Acidity of Contents of Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	8	0	10
After 30 minutes	0	11	0	18
After 45 minutes	0	15	0	16
After 60 minutes	0	6	0	8
Total	0	40	0	52

TABLE 8.—*Acidity of Contents of Stomach After Ingestion of Epinephrine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	12	0	9
After 30 minutes	0	10	0	12
After 45 minutes	0	7	0	8
After 60 minutes	0	6	0	5
Total	0	35	0	34

eight months. He first consulted a chiropractor whose manipulation of the vertebrae did not improve his condition. When first examined by a physician, a mass about as large as a golf ball was found in the epigastrium, above and to the right of the umbilicus. Roentgen-ray diagnosis was carcinoma of the pylorus. Gastric analysis and other laboratory observations confirmed this diagnosis. Three hundred and twenty cubic centimeters of foul smelling contents of the stomach was aspirated while the patient was fasting; there was not any free hydrochloric acid found, the total acidity was 15. The results of the gastric analysis are shown in table 7.

The result of the gastric analysis after the administration of epinephrine with the first test breakfast are shown in table 8.

Thus the torpor of organic origin is unaffected by the administration of epinephrine. The results of gastric analysis of the same patient after injection of atropine at the time of the first test breakfast is shown in table 9.

The results of gastric analysis in this patient after the administration of pilocarpine are indicated in table 10.

TABLE 9.—*Acidity of Contents of Stomach After Ingestion of Atropine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	6	0	6
After 30 minutes	0	10	0	9
After 45 minutes	0	12	0	9
After 60 minutes	0	8	0	7
Total	0	36	0	31

TABLE 10.—*Acidity of Contents of Stomach After Ingestion of Pilocarpine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	4	0	4
After 30 minutes	0	6	0	6
After 45 minutes	0	8	0	6
After 60 minutes	0	8	0	6
Total	0	36	0	31

TABLE 11.—*Acidity of Contents of the Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	8	10	12
After 30 minutes	8	21	15	20
After 45 minutes	12	24	32	45
After 60 minutes	16	20	27	36
Total	36	73	84	113

Evidence is presented then, that where the torpor is organic, neither atropine, pilocarpine nor epinephrine can stimulate the gastric cells to secretion.

CASE 4.—K. D., aged 47, complained of epigastric discomfort, feeling of fulness, eructation of gas with fetid odor, bad taste in the mouth, occasional nausea and vomiting. He was generally constipated, but occasionally had attacks of diarrhea. A diagnosis of pulmonary tuberculosis was made. The results of gastric analysis are shown in table 11. Twenty-two cubic centimeters of the contents of the stomach was aspirated while the patient was fasting; the free hydrochloric acid was found to be 8 and the total acidity was found to be 24.

The gastric reaction in the foregoing case falls into the inert hyposecretory type. A few days later, atropine was injected into the patient at the time of the first test breakfast, with the results shown in table 12.

After atropine has been given, an inert hyposecretory type of secretion remains unchanged as to type, but the work of the gastric cells

TABLE 12.—*Acidity of Contents of Stomach After Ingestion of Atropine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	8	0	9
After 30 minutes	0	10	4	14
After 45 minutes	4	16	12	28
After 60 minutes	6	22	32	52
Total	10	56	48	103

TABLE 13.—*Acidity of Contents of Stomach After Ingestion of Epinephrine Hydrochloric Acid*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	6	6	14
After 30 minutes	0	6	11	20
After 45 minutes	8	18	18	26
After 60 minutes	12	23	16	21
Total	20	53	53	81

TABLE 14.—*Acidity of Contents of Stomach After Ingestion of Pilocarpine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	12	0	4
After 30 minutes	0	8	0	6
After 45 minutes	0	8	0	10
After 60 minutes	0	4	0	6
Total	0	32	0	26

is considerably diminished by its use. One must assume that in this case, secreting cells that are already fatigued, react with even less work when further stimulated. As stated previously the phase of activity in which the drug finds the cell when it reaches it, determines whether the drug produces increased or diminished secretion.

The foregoing test was repeated using epinephrine instead of atropine, with the results shown in table 13.

The effect of epinephrine in this case, is essentially the same as that of atropine. Pilocarpine was next administered after an interval of a few days, with the results shown in table 14.

The overstimulation of gastric cells that were already fatigued, resulted in complete inhibition due to overloading the cell. In short, functional torpor has been produced in this case of an inert hyposecretion by the use of pilocarpine.

CASE 5.—T. L., aged 32, a married woman, complained of weakness, visual disturbance and loss of appetite. Her skin had a lemon-yellow tint. The result

TABLE 15.—*Acidity of Contents of Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	16	0	31
After 30 minutes	0	22	0	32
After 45 minutes	0	21	0	32
After 60 minutes	0	20	0	empty
Total	0	79	0	95

TABLE 16.—*Acidity of Contents of Stomach After Ingestion of Atropine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	17	0	29
After 30 minutes	0	18	0	28
After 45 minutes	0	28	0	32
After 60 minutes	no contents	20	0	29
Total	0	65	0	118

TABLE 17.—*Acidity of Contents of Stomach After Ingestion of Pilocarpine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	23	0	23
After 30 minutes	0	26	0	29
After 45 minutes	0	21	0	25
After 60 minutes	0	23	0	25
Total	0	93	0	93

of the Wassermann reaction was negative. Red blood cells numbered 2,300,000; white blood cells 4,000, and hemoglobin 40 per cent. The smear taken showed every symptom of pernicious anemia. Except for evidence of extreme anemia, the remainder of the examination was essentially normal. There was not any fasting contents obtained.

After the administration of atropine, the results of the gastric analysis were as shown in table 16.

After the administration of pilocarpine the results of gastric analysis are given in table 17.

After the administration of epinephrine, gastric analysis was made. The results are shown in table 18.

In this case of pernicious anemia, the gastric cells are totally exhausted and cannot be stimulated to activity, whether the stimulus be a normal one, such as the meat broth, or whether it be reinforced by a drug such as atropine, epinephrine or pilocarpine.

TABLE 18.—*Acidity of Contents of the Stomach After Ingestion of Epinephrine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	23	0	38
After 30 minutes	0	26	0	30
After 45 minutes	0	28	0	30
After 60 minutes	0	24	0	25
Total	0	101	0	123

TABLE 19.—*Acidity of Contents of the Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	25	42	12	34
After 30 minutes	60	77	39	53
After 45 minutes	80	93	60	72
After 60 minutes	52	66	40	52
Total	217	278	153	211

TABLE 20.—*Acidity of the Contents of the Stomach After Ingestion of Atropine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	0	14	0	12
After 30 minutes	16	25	14	24
After 45 minutes	52	63	62	74
After 60 minutes	47	54	51	63
Total	115	156	127	173

CASE 6.—W. K., a man, aged 41, complained of pain in the epigastrium, which usually came on from one to two hours after eating. This pain was aggravated by certain foods taken. He did not vomit but had sour eructations. The results of a physical examination revealed tenderness and voluntary rigidity just above the umbilicus, a large dilated stomach and blood in the stool. Roentgen-ray diagnosis was ulcer of the stomach situated near the pylorus. The results of gastric analysis are shown in table 19. Eighty cubic centimeters of the contents of the stomach was aspirated while the patient was fasting; the free hydrochloric acid was found to be 28, and the total acidity 42.

The patient demonstrates the asthenic hyperacid type of secretion.

After the administration of atropine, gastric analysis was made. The results are shown in table 20.

Thus, after atropine is given, the type of secretion is nearer that of the normal, although the hyperacidity persists. It has been observed clinically that atropine produces aggravation of symptoms in some cases of gastric ulcer, whereas in others it apparently produces relief from symptoms. This difference of action can be explained by stating that in those cases in which the gastric cells have retained their power of accommodation, atropine, by converting the asthenic hyperacid type of secretion into the normal type, produces relief; but in cases in which the dysfunction has reached a point where conversion of one type to another is no longer possible, atropine either does not have any effect, or else may serve to aggravate the dysfunction.

TABLE 21.—*Acidity of Contents of Stomach After Ingestion of Epinephrine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	12	19	12	23
After 30 minutes	39	50	20	31
After 45 minutes	43	54	47	54
After 60 minutes	38	47	33	43
Total	132	170	112	151

TABLE 22.—*Acidity of Contents of Stomach After Ingestion of Pilocarpine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	14	22	38	52
After 30 minutes	24	32	52	68
After 45 minutes	42	54	68	76
After 60 minutes	32	45	64	70
Total	112	153	222	266

After the administration of epinephrine, gastric analysis gave the results shown in table 21.

After epinephrine is given there is a decrease in the acidity, but the asthenic type of the secretion remains.

Pilocarpine was next administered. The following results of gastric analysis are shown in table 22.

Here, then, the pilocarpine has converted an asthenic type of secretion into an inert type.

CASE 7.—H. F., a man, aged 26, arrived in Detroit from Argentina three days before his first visit to me. While on the boat coming to Detroit he developed jaundice. When first seen, the skin and sclerae were yellow; the urine was dark and gave a postive reaction to bile. The stools were clay colored. The results of a physical examination were otherwise normal. The jaundice gradually disappeared, and the condition was diagnosed as catarrhal jaundice.

The gastric analyses recorded in table 23 were made while the jaundice was still present. Thirty-two cubic centimeters of the contents of the stomach was aspirated while the patient was fasting; the free hydrochloric acid was found to be 15, and the total acidity 36.

This is the hypersecretory-asthenic type of gastric secretion, usually noted in cases of catarrhal jaundice, which indicates that the gastric cells are in a state of irritation and due to this irritation, are approach-

TABLE 23.—*Acidity of Contents of Stomach After Ingestion of Food*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	23	40	23	42
After 30 minutes	56	76	51	71
After 45 minutes	68	82	48	68
After 60 minutes	58	72	43	53
Total	205	270	165	234

TABLE 24.—*Acidity of Contents of Stomach After Ingestion of Epinephrine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	10	24	34	57
After 30 minutes	28	35	60	72
After 45 minutes	60	75	72	84
After 60 minutes	68	82	58	66
Total	166	216	224	279

TABLE 25.—*Acidity of Contents of the Stomach After Ingestion of Pilocarpine*

	First Breakfast		Second Breakfast	
	Free Hydrochloric Acid	Total Acidity	Free Hydrochloric Acid	Total Acidity
After 15 minutes	4	12	11	21
After 30 minutes	24	30	38	52
After 45 minutes	30	39	60	75
After 60 minutes	33	40	54	66
Total	91	127	163	214

ing the point of fatigue, as may be seen from the decrease in the secretion with the second test breakfast. After epinephrine was administered gastric analysis was made. The results are shown in table 24.

Although, after epinephrine was given, the hyperacidity persisted, the type of secretion approached more closely the normal.

As in the previous cases, pilocarpine was administered. The observations made in this case are listed in table 25.

Pilocarpine has converted a hypersecretory asthenic type of secretion into a normosecretory inert type. One can assume that the pilo-

carpine, reaching irritated gastric cells that were already near fatigue, further depressed their secretory activity by overstimulation. The patient's jaundice did not persist long enough to determine the effect of atropine on his gastric secretion.

CONCLUSIONS

1. Evidence is presented to show that one type of gastric secretion can be converted into a different type of secretion by the use of atropine, epinephrine or pilocarpine.

2. The use of these drugs is suggested as a diagnostic measure in differentiating functional from organic achylia.

3. Since the reserve energy of the cell depends on the functional phase or degree of fatigue of the cell at the time that stimulation is instigated, the use of atropine, epinephrine and pilocarpine furnishes a means of estimating the reserve energy of the secreting gastric cells.

4. An explanation is offered, reconciling previous apparently contradictory observations on the action of atropine, epinephrine and pilocarpine on the stomach.

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AREA OF THE BODY SURFACE AND MEASUREMENTS OF THE NORMAL HEART

A PRELIMINARY REPORT *

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There has been insufficient study of the measurements of the normal heart. The number of cases of normal hearts measured in men are comparatively few, while the number for women and children are still less.[1] The averages and ranges of measurements are usually given for weight, height, age and diameter of the chest; but, as suggested by Cohn [2] after a study of his curves and those of Dietlen [3] and Schieffer,[4] in judging the normality of a given heart, it is necessary to have more than a single criterion, such as weight or height. A review of the literature on measurements of normal hearts fails to show any classification of the persons studied in regard to whether they were above, below or of average or ideal weight for the respective height and age.

According to the investigations of Deutsch and Kauf,[1] there is a direct relation between weight and the diameter of the chest. Since both height and weight can be used for the determination of the area of the body surface,[5] I propose to investigate the possibility of using the area of the body surface as a criterion for judging the normality of a given heart. Not only does body surface area incorporate weight, but there appears to be a relation between this area and the size of the capillary bed. Since the size of the entire capillary bed depends on the size of the body and its organs, as does the area of the body surface, it is reasonable to suppose that a direct relation exists between the area of the body surface and the size of the capillary bed. Also as, quoting

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4. Schieffer: Ueber den Einfluss des Militardienstes auf die Herzgrosse, Deutsches Arch. f. klin. Med. **92**:392, 1908.

5. DuBois, E. F.: Basal Metabolism in Health and Disease, p. 143; chart by W. M. Boothby and R. B. Sandiford, Philadelphia, Lea & Febiger, 1924.

from Hershfelder,[6] "Josue"[7] has shown, repeated injections of epinephrine in the rabbit are followed by a permanent rise in blood pressure. Aubertin[8] has found hyperplasia of the suprarenals in arteriosclerotic persons, while A. E. Cohn found the same condition in patients without arteriosclerosis. Moreover, Fraenkel[9] found an increase of epinephrine in the blood of only a small percentage of patients with hypertension. It therefore seems possible that hypertrophy of the heart and arteriosclerosis may often be the result of a hypersecretion of epinephrine, perhaps also of some other internal secretion. Since Herschfelder found that epinephrine causes a constriction of the peripheral vessels and capillary bed[6] with increased heart effort, while Dale, Laidlaw and Richards,[10] who made experiments with histamine, found a dilatation of the capillaries and a pooling of the blood in the capillary bed and decreased cardiac output, which according to MacKenzie[11] is a cause of heart failure, it is reasonable to suggest that there is possibly a closer relation between the area of the body surface and the size of the heart than just the fact that this area incorporates height and weight.

In this report I have not used my own figures, but have taken those of the 204 soldiers investigated by Cohn[2] and the 277 investigated by Smith,[12] making altogether 481 cases studied. This material was used because there were complete data as to height, weight, age, etc., for each case. In the determination of the area of the body surface, the chart from DuBois[5] was used, while in the determination of the ideal body weight, figures commonly used by the insurance companies were employed (table 3).

METHOD

The area of the body surface was computed in each of the 481 cases; these were classified into groups with areas of from 1.4 square meters to 1.49 square meters inclusive and so on up to 2.1 square meters, with a range of 0.1 square meter in each group (table 1). The average and range of the measurements of the transverse diameter of the hearts in each group were computed; also those

6. Herschfelder, J. O.: Disease of the Heart and Aorta, Philadelphia, J. B. Lippincott Company, 1918, pp. 268 and 355.

7. Josue, O.: Atherome aortique experimental par injections repetées d'adrenaline dans les veins, Compt. rend. Soc. de biol. **55**:1374, 1903.

8. Aubertin and Ambaid: Lésions des capsules surrénales dans les néphrites aves hypertension, Bull. et mém. Soc. méd. d. hôp. de Paris **19**:175, 1904.

9. Fraenkel: Arch. f. exper. Path. u. Pharmakol. **60**:394, 1909.

10. Dale, Laidlaw and Richards: J. Physiol. **52**:110, 1918; **52**:355, 1919.

11. MacKenzie, Sir James: Diseases of the Heart, New York, Oxford University Press, 1925, p. 26.

12. Smith, B.: Teleroentgen Measurements of the Hearts of Normal Soldiers, Arch. Int. Med. **25**:522 (May) 1920.

TABLE 1.—*Comparison of Actual and Ideal Area of Body Surface and Weight in 481 Cases Classified in Groups*

Actual Surface Area, Sq. Meters	Ideal Weight Surface Area, Sq. Meters	Transverse Diameter, Cm.	Actual Weight, Kg.	Ideal Weight, Kg.	Height, Cm.	Age
1.47	1.42	13.6	53	47	152	29
1.51	1.46	13.4	53	48	157	21
1.58	....	12	54	..	164	40
1.55	....	11.9	54	..	162	20
1.54	1.47	12.8	55	49	158	29
1.55	1.47	13.9	56	49	158	25
1.58	1.48	12.3	57	48	160	19
1.55	1.41	12.6	58	46	155	30
1.59	1.50	12.7	58	50	160	28
1.58	1.48	12.4	59	49	160	24
1.65	....	13.8	56	..	173	24
1.64	....	12.3	56	..	171	27
1.62	....	11.2	56	..	168	22
1.63	....	12.6	57	..	168	24
1.66	....	11.5	57	..	172	23
1.61	....	11.2	57	..	165	23
1.61	1.53	12.8	58	51	163	24
1.64	....	11.4	58	..	168	25
1.65	....	11.2	58	..	170	25
1.68	....	11.5	59	..	169	21
1.64	1.58	11.5	59	53	166	25
1.65	....	12.5	59	..	167	23
1.69	....	12.4	60	..	177	25
1.62	1.52	13.3	60	51	162	23
1.64	1.56	13.3	60	53	164	29
1.68	....	12.5	60	..	170	24
1.68	1.50	12.8	61	50	161	27
1.69	1.61	10.5	61	55	168	29
1.62	1.56	13	61	53	164	25
1.65	1.52	11.2	62	51	163	24
1.68	1.57	14.2	62	55	166	30
1.67	1.54	14	63	52	163	33
1.67	1.54	13.5	63	52	163	28
1.68	1.54	12.8	63	52	164	21
1.69	1.56	12	64	53	164	29
1.61	....	12.1	55	..	168	27
1.65	....	11.6	55	..	173	21
1.60	....	11.6	55	..	165	23
1.63	1.53	12.7	57	51	163	24
1.61	....	11.7	57	..	165	31
1.62	....	12.4	57	..	168	20
1.68	....	12.5	57	..	175	20
1.61	1.51	12.6	58	50	163	20
1.65	1.51	12.8	58	50	163	20
1.65	1.54	12.7	58	52	163	30
1.62	....	12.6	58	..	165	30
1.64	1.57	12.5	58	52	168	19
1.63	1.55	13.5	59	52	165	23
1.63	1.56	11.5	59	53	165	25
1.63	1.56	12.6	59	53	165	29
1.69	....	12.8	58	..	173	28
1.60	1.49	12.4	59	49	160	24
1.63	1.53	12.1	59	51	163	22
1.66	....	12.6	59	..	168	24
1.66	....	12.8	59	..	168	20
1.67	....	13.6	59	..	170	23
1.67	....	12.7	59	..	170	23
1.67	....	12.8	59	..	170	30
1.69	....	12.7	59	..	173	24
1.69	....	12.9	59	..	173	27
1.69	....	12.7	59	..	173	28
1.69	....	12.7	59	..	173	28
1.62	1.47	12.7	61	48	160	29
1.62	1.50	11.9	61	50	160	26
1.64	1.54	10.1	61	52	163	26
1.66	1.55	12.6	61	52	165	24
1.68	1.58	12.8	61	54	168	19
1.68	1.61	12.2	61	55	168	26
1.68	1.61	11.7	61	55	168	28
1.68	1.61	12.5	61	55	168	30
1.69	1.62	11.4	61	56	170	23
1.69	1.63	12.7	61	56	170	28

TABLE 1.—*Comparison of Actual and Ideal Area of Body Surface and Weight in 481 Cases Classified in Groups—Continued*

Actual Surface Area, Sq. Meters	Ideal Weight Surface Area, Sq. Meters	Transverse Diameter, Cm.	Actual Weight, Kg.	Ideal Weight, Kg.	Height, Cm.	Age
1.60	....	13.7	62	..	157	25
1.65	1.54	12.9	62	52	163	28
1.60	1.60	11.5	62	54	168	22
1.60	1.61	13.2	62	55	168	25
1.60	1.61	13.1	62	55	168	28
1.60	....	11.3	63	..	155	26
1.64	1.49	11.8	63	50	160	30
1.67	1.54	11.4	63	52	163	27
1.69	1.48	12.9	67	49	160	22
1.70	....	12.7	60	..	172	25
1.70	....	12.7	59	..	175	19
1.71	....	11.3	60	..	174	29
1.77	....	12.5	60	..	183	25
1.71	....	10.8	60	..	174	21
1.70	....	12.5	60	..	173	23
1.72	....	11.8	61	..	174	24
1.73	....	11.7	61	..	176	27
1.73	....	11.9	62	..	173	29
1.71	....	12.3	62	..	171	26
1.73	....	12.5	62	..	173	25
1.71	....	13	62	..	170	29
1.74	1.64	12.8	63	55	172	50
1.75	....	13.8	63	..	174	40
1.71	1.61	13.5	63	55	169	21
1.71	1.63	12	63	56	169	28
1.77	....	12.7	63	..	178	23
1.72	1.62	11.3	63	55	170	23
1.73	1.65	10.5	63	56	172	20
1.71	1.60	14.4	64	55	167	30
1.70	1.59	11.8	63	54	167	24
1.76	....	12.8	64	..	174	23
1.71	1.60	12.7	64	55	167	31
1.75	1.67	13.4	64	57	173	24
1.78	....	12.2	64	..	176	21
1.71	1.59	12.5	64	54	167	24
1.74	1.64	12.8	64	56	171	26
1.72	1.61	13.2	64	55	168	28
1.79	....	14.2	65	..	177	28
1.78	....	13.3	65	..	175	28
1.73	1.57	12.8	65	52	168	20
1.74	1.61	11.8	65	54	170	20
1.78	1.72	12.8	65	59	176	21
1.70	1.56	12.3	65	53	164	27
1.76	1.67	12.8	65	58	172	27
1.74	1.63	12.7	65	55	170	23
1.74	1.62	11.2	65	54	170	20
1.72	1.55	11.6	66	52	165	22
1.71	1.56	13.5	66	53	164	27
1.73	1.61	12.4	66	55	167	26
1.71	1.56	12.6	66	52	165	21
1.70	1.49	14.5	67	50	161	25
1.79	1.69	14.6	67	58	173	29
1.74	1.60	13.7	67	55	167	25
1.74	1.60	14.4	67	55	167	26
1.75	1.61	14	67	55	168	27
1.76	1.62	13.2	67	55	169	23
1.77	1.63	15	67	55	170	24
1.76	1.57	13.5	68	52	167	49
1.78	1.63	15	68	55	171	24
1.78	1.63	13.4	68	55	171	21
1.77	1.63	13.8	68	56	170	26
1.77	1.59	12.9	69	54	167	22
1.78	1.63	14.8	69	56	169	26
1.78	1.60	15	71	55	167	26
1.78	1.56	12.4	72	52	165	23
1.71	....	12.4	58	..	178	23
1.71	....	11.8	58	..	178	24
1.73	....	12.5	58	..	180	24
1.72	....	12.9	59	..	175	19
1.72	....	12.8	59	..	175	21
1.72	....	12.7	59	..	175	27
1.72	....	12.8	59	..	175	30
1.72	....	12.3	59	..	178	22

TABLE 1.—*Comparison of Actual and Ideal Area of Body Surface and Weight in 481 Cases Classified in Groups—Continued*

Actual Surface Area, Sq. Meters	Ideal Weight Surface Area, Sq. Meters	Transverse Diameter, Cm.	Actual Weight, Kg.	Ideal Weight, Kg.	Height, Cm.	Age
1.72	....	12.5	59	..	178	27
1.72	....	14	59	..	178	30
1.72	....	12.7	60	..	175	23
1.71	....	12.1	61	..	173	20
1.71	....	13.1	61	..	173	22
1.71	....	13.2	61	..	173	23
1.71	....	11.6	61	..	173	24
1.73	....	11.3	61	..	175	19
1.73	....	10.6	61	..	175	22
1.73	....	11.2	61	..	175	22
1.73	....	11.8	61	..	175	23
1.73	....	12	61	..	175	27
1.75	....	12.4	61	..	178	20
1.75	....	11.6	61	..	178	21
1.75	....	12	61	..	178	23
1.75	....	12.4	61	..	178	30
1.77	....	12.8	61	..	180	23
1.77	....	12.1	61	..	180	24
1.77	....	11.8	61	..	180	30
1.70	1.64	11.4	62	56	170	26
1.72	1.66	11.1	62	56	173	19
1.74	....	12.6	62	..	175	24
1.75	....	11.8	62	..	178	22
1.76	....	12.2	62	..	178	23
1.76	....	11.1	62	..	178	28
1.76	....	12.6	62	..	178	29
1.70	1.60	12.1	63	54	168	23
1.70	1.61	11.8	63	55	168	20
1.72	1.62	11.5	63	55	170	22
1.72	1.62	13.6	63	55	170	22
1.72	1.62	11.7	63	55	170	23
1.72	1.62	11.7	63	55	170	24
1.74	1.66	13.2	63	56	173	20
1.74	1.67	11.2	63	57	173	22
1.74	1.67	11.6	63	57	173	23
1.74	1.67	11.8	63	57	173	23
1.74	....	11.5	63	..	173	25
1.74	....	12	63	..	173	25
1.74	....	12.7	63	..	173	26
1.74	....	12	63	..	173	28
1.75	....	10.6	63	..	175	22
1.75	....	11.1	63	..	175	27
1.75	....	11.4	63	..	175	27
1.78	....	11	63	..	178	19
1.78	....	12.2	63	..	178	23
1.78	....	11.1	63	..	178	24
1.78	....	12.9	63	..	178	25
1.78	....	12	63	..	178	27
1.78	....	12.1	63	..	178	28
1.72	1.57	11.7	64	57	168	20
1.72	1.60	12.6	64	54	168	22
1.73	1.62	12.3	64	55	170	21
1.73	1.62	11.7	64	55	170	23
1.73	1.62	12.6	64	55	170	24
1.75	1.67	12.4	64	57	173	21
1.75	1.67	12	64	57	173	24
1.77	....	12.7	64	..	175	22
1.77	....	12.6	64	..	175	26
1.77	....	12.4	64	..	175	26
1.79	....	12.8	64	..	178	23
1.79	....	12.4	64	..	178	25
1.79	....	13.1	64	..	178	25
1.79	....	12.3	64	..	178	26
1.70	1.58	12.6	65	52	165	23
1.72	1.60	13.2	65	54	168	23
1.72	1.61	13.2	65	55	168	27
1.74	1.62	12.8	65	55	170	22
1.76	1.65	13.1	65	56	173	19
1.76	1.68	12.6	65	58	173	25
1.76	1.68	13.4	65	58	173	26
1.78	1.70	12.5	65	58	175	20
1.78	....	13	65	..	175	26
1.75	1.62	13.7	66	55	170	23
1.75	1.60	13.4	67	54	168	24

TABLE 1.—*Comparison of Actual and Ideal Area of Body Surface and Weight in 481 Cases Classified in Groups—Continued*

Actual Surface Area, Sq. Meters	Ideal Weight Surface Area, Sq. Meters	Transverse Diameter, Cm.	Actual Weight, Kg.	Ideal Weight, Kg.	Height, Cm.	Age
1.75	1.61	13.6	67	55	168	26
1.75	1.61	12.8	67	55	168	29
1.76	1.63	13.6	67	56	170	29
1.76	1.63	12.6	67	56	170	26
1.79	1.60	12.9	67	58	173	29
1.73	1.56	13	68	52	165	22
1.76	1.61	13.9	68	55	168	26
1.78	1.61	13.3	68	54	170	20
1.78	1.62	13.4	68	55	170	22
1.78	1.61	13.5	69	55	168	27
1.78	1.61	13.6	69	55	168	31
1.79	1.62	13.9	69	55	170	21
1.79	1.62	13.5	69	56	170	26
1.78	1.61	13.5	70	56	168	27
1.81	....	11.2	64	..	181	29
1.84	....	13.2	66	..	182	25
1.82	....	12.3	66	..	179	19
1.81	1.73	13.7	67	60	176	27
1.81	1.71	12.4	67	59	175	23
1.81	1.72	12.4	67	60	175	28
1.81	1.71	12.8	68	59	175	24
1.80	1.68	11.8	68	58	174	18
1.80	1.69	12.8	68	54	174	20
1.81	1.72	14	68	60	175	26
1.83	1.71	12.1	68	59	176	23
1.84	1.74	13	68	61	178	23
1.82	1.71	15.7	69	59	175	42
1.86	....	12.7	69	..	180	26
1.82	1.71	13.8	69	60	174	31
1.84	1.74	12.6	69	61	177	23
1.84	1.75	11.8	69	62	177	25
1.88	....	12.8	69	..	182	28
1.80	1.64	14.8	69	56	171	30
1.84	....	12.1	67	..	180	27
1.80	1.66	13.8	68	56	173	18
1.80	1.69	13.4	68	58	173	25
1.80	1.69	12.7	68	58	173	29
1.81	1.72	13.3	68	60	175	26
1.83	1.75	13.7	68	61	178	24
1.83	....	13.4	68	..	178	29
1.85	....	13.4	68	..	180	20
1.87	....	13.6	68	..	183	40
1.81	1.68	13.6	69	58	172	26
1.84	1.75	12.2	69	62	177	28
1.86	....	12.3	69	..	180	26
1.83	1.71	13.5	70	60	174	31
1.87	....	12	70	..	180	30
1.81	1.64	13.8	70	56	171	30
1.84	1.72	15	70	59	176	40
1.84	1.73	13.3	70	60	176	29
1.80	1.64	13.9	70	56	170	25
1.84	1.71	13	70	59	175	24
1.84	1.71	11.8	70	59	175	22
1.84	1.70	13	70	58	175	18
1.82	1.66	13.7	71	57	172	22
1.80	1.61	14	71	55	169	36
1.81	1.64	14.2	71	56	170	29
1.86	1.75	13.3	71	62	177	34
1.84	1.68	14	71	58	172	27
1.87	1.75	12.1	71	61	178	23
1.84	1.66	11.3	71	57	172	23
1.89	1.79	12.7	72	63	179	24
1.80	1.59	14.2	72	54	167	24
1.85	1.70	14	72	59	174	22
1.88	1.75	13	72	61	178	24
1.85	1.69	12.4	72	58	174	20
1.86	1.71	14.7	72	60	174	29
1.87	1.75	13.4	72	62	177	26
1.84	1.67	12.8	72	57	173	21
1.85	1.68	14.5	73	58	173	25
1.89	1.75	14.1	73	61	178	21
1.88	1.71	14.1	74	60	174	28
1.82	1.56	14.6	74	52	160	22

TABLE 1.—*Comparison of Actual and Ideal Area of Body Surface and Weight in 481 Cases Classified in Groups—Continued*

Actual Surface Area, Sq. Meters	Ideal Weight Surface Area, Sq. Meters	Transverse Diameter, Cm.	Actual Weight, Kg.	Ideal Weight, Kg.	Height, Cm.	Age
1.85	1.62	13.7	74	55	171	24
1.86	1.66	12.3	74	59	172	23
1.86	1.68	13	74	58	172	25
1.89	1.71	14.7	75	60	175	25
1.85	1.64	13.2	75	56	170	28
1.88	1.68	16	75	58	173	25
1.87	1.68	12	75	58	172	25
1.82	1.56	13	75	53	165	27
1.89	1.72	13.2	75	60	175	30
1.88	1.70	12.7	75	59	174	21
1.89	1.71	11	75	59	175	24
1.80	1.80	13.7	64	..	180	23
1.80	....	13.8	64	..	180	26
1.80	....	13.3	64	..	180	27
1.86	....	13.6	67	..	183	31
1.80	1.67	13.5	68	57	173	22
1.80	1.68	13.6	68	58	173	25
1.81	1.72	11.9	68	60	175	25
1.81	1.72	12.7	68	60	175	26
1.83	....	13.4	68	..	178	27
1.83	....	13.6	68	..	178	29
1.88	....	13.6	68	..	184	28
1.81	1.69	13.6	69	58	173	29
1.82	1.70	12.7	69	58	175	20
1.84	1.75	13.5	69	61	178	21
1.84	1.75	11.4	69	61	178	24
1.86	....	12.9	69	..	180	23
1.86	....	13.1	69	..	180	26
1.80	1.62	13.5	70	55	170	22
1.82	1.67	13.5	70	57	173	22
1.83	1.71	13.5	70	59	175	21
1.85	1.71	13.4	70	59	175	24
1.83	1.72	13.5	70	60	175	25
1.83	1.72	13.4	70	60	175	28
1.83	1.72	13.5	70	60	175	28
1.83	1.72	13.6	70	60	175	28
1.85	1.75	13.4	70	61	178	22
1.85	1.75	13.3	70	61	178	20
1.85	1.75	13.6	70	61	178	23
1.85	1.75	13.4	70	62	178	25
1.85	1.75	13.4	70	62	178	31
1.85	1.75	13.3	70	62	178	34
1.80	1.60	13.5	71	54	168	24
1.81	1.64	13.4	71	56	170	27
1.81	1.64	13.7	71	56	170	27
1.83	1.68	11.6	71	58	173	26
1.83	1.68	13.5	71	58	173	29
1.85	1.71	12.9	71	59	175	21
1.84	1.72	13.3	71	60	175	26
1.84	1.72	13.4	71	60	175	32
1.87	1.75	13.4	71	62	178	27
1.87	1.75	13.6	71	62	178	28
1.87	1.75	13.4	71	62	178	29
1.87	1.75	13.2	71	62	178	30
1.88	1.81	13.4	71	62	180	28
1.81	1.61	13.4	72	55	168	30
1.82	1.64	13.8	72	56	170	26
1.85	1.67	13.5	72	57	173	24
1.85	1.68	13.4	72	58	173	28
1.86	1.71	13.7	72	59	175	21
1.88	1.75	13.5	72	61	178	24
1.83	1.64	13.7	73	56	170	26
1.83	1.64	14.2	73	56	170	32
1.87	1.72	13.5	73	60	175	25
1.89	1.75	13.4	73	62	178	26
1.80	....	12.9	65	..	178	36
1.81	....	11.4	65	..	180	23
1.81	....	13.3	65	..	180	27
1.84	....	13.7	65	..	184	23
1.84	....	12.8	65	..	184	28
1.81	....	12.9	66	..	178	23
1.81	....	12.2	66	..	178	26
1.82	....	13.6	66	..	180	26
1.82	....	13.6	67	..	178	21

TABLE 1.—*Comparison of Actual and Ideal Area of Body Surface and Weight in 481 Cases Classified in Groups—Continued*

Actual Surface Area, Sq. Meters	Ideal Weight Surface Area, Sq. Meters	Transverse Diameter, Cm.	Actual Weight, Kg.	Ideal Weight, Kg.	Height, Cm.	Age
1.82	....	12.9	67	..	178	22
1.82	....	13.5	67	..	178	23
1.82	....	13	67	..	178	31
1.84	....	13.4	67	..	180	24
1.80	1.53	13.7	75	52	163	31
1.84	1.66	13.9	75	54	168	23
1.88	1.68	13.7	75	58	173	28
1.88	1.68	13.6	75	58	173	29
1.85	1.60	13.7	76	54	168	23
1.89	1.67	13.6	76	57	173	23
1.84	1.55	14.3	77	52	165	23
1.86	1.61	13.7	77	55	168	26
1.89	1.64	13.7	79	56	170	25
1.88	1.56	13.5	81	53	165	26
1.90	....	12.8	70	..	184	27
1.91	1.75	13.3	74	62	178	27
1.96	....	12.7	74	..	186	23
1.91	1.72	14.5	76	60	176	25
1.94	1.80	12.3	77	64	179	28
1.96	1.82	12.8	77	64	181	30
1.90	1.67	14.2	78	59	173	24
1.90	1.83	13.3	71	64	183	19
1.90	1.80	13.3	72	64	180	29
1.90	1.80	13.6	72	64	180	31
1.92	....	13.5	72	..	183	25
1.93	....	13.8	72	..	184	25
1.93	1.84	13.5	73	66	183	30
1.90	1.74	13.7	74	61	178	23
1.91	1.75	13.5	74	62	178	28
1.92	1.79	13.8	74	63	180	24
1.92	1.80	13.8	74	64	180	27
1.92	1.80	13.9	74	64	180	30
1.94	1.84	13.8	74	66	183	31
1.92	1.74	13.5	75	61	178	24
1.92	1.75	13.9	75	62	178	24
1.93	1.79	13.5	75	63	180	24
1.93	1.80	13.5	75	64	180	29
1.93	1.80	13.6	75	64	180	29
1.93	1.80	13.8	75	64	180	30
1.93	1.80	13.7	75	64	180	31
1.96	1.88	13.7	75	68	184	27
1.96	1.88	13.5	75	68	184	28
1.93	1.74	13.4	76	61	178	23
1.93	1.75	13.5	76	62	178	31
1.94	1.79	13.8	76	63	180	23
1.94	1.80	13.7	76	64	180	29
1.94	1.80	13.7	76	64	180	29
1.97	1.82	13.6	76	63	184	23
1.90	1.68	13.8	77	58	173	25
1.90	1.68	13.4	77	58	173	28
1.91	1.72	13.8	77	60	175	25
1.94	1.74	13.7	77	61	178	24
1.94	1.75	13.6	77	62	178	27
1.95	1.80	13.4	77	64	180	27
1.91	1.68	14	78	58	173	26
1.95	1.75	13.5	78	62	178	27
1.95	1.74	14.2	79	60	178	20
1.99	1.84	13.2	79	66	183	25
1.97	1.75	13.9	80	62	178	25
1.98	1.80	13.5	80	64	180	30
1.98	1.75	14.3	81	62	178	28
1.99	1.80	13.3	81	64	180	30
1.96	1.68	13.5	82	58	173	25
2.01	1.80	14.3	84	64	180	27
2.02	1.83	12.5	83	65	182	21
2	1.80	13.8	83	64	179	24
2.04	1.80	13.8	86	64	180	26
2	1.88	13.5	79	68	184	25
2	1.75	13.8	83	62	178	25
2	1.75	13.6	83	62	178	29
2.08	1.87	13.7	84	67	184	38

for persons of ideal weight and those for persons with above-ideal weight, and a comparison was made (table 2). A variation of 10 per cent was allowed before classification as above or below ideal weight (table 3).

The above-ideal weight cases were subdivided into subgroups according to what the area of the body surface would have been, if the weight had been ideal. These figures were compared with averages and limits of transverse diameters in all the groups, in the ideal weight group and in the entire above weight groups; they were also compared with each other (table 4).

TABLE 2.—*Average and Range of Heart Measurements of Each Group*

Surface Area Group, Sq. Meters		Ideal Weight, Cm.	Above Ideal Weight, Cm.	Entire Group, Cm.
1.4 to 1.49	Average	.....	13.6	13.6
	Number	.....	1	1
	Limits	.....	.....	.....
1.5 to 1.59	Average	11.9	12.8	12.6
	Number	2	7	9
	Limits	11.9 - 12	12.3 - 13.9	11.9 - 13.9
1.6 to 1.69	Average	12.3	12.4	12.4
	Number	31	40	71
	Limits	11.2 - 13.8	10.1 - 14.2	10.1 - 14.2
1.7 to 1.79	Average	12.2	12.8	12.5
	Number	71	81	152
	Limits	10.6 - 14.2	11.3 - 16	10.5 - 15
1.8 to 1.89	Average	12.9	13.3	13.9
	Number	33	115	148
	Limits	11.2 - 13.8	11.3 - 16	11 - 16
1.9 to 1.99	Average	13.2	13.6	13.5
	Number	4	45	49
	Limits	12.8 - 13.8	12.3 - 14.5	12.3 - 14.5
2 to 2.09	Average	.....	13.6	13.6
	Number	.....	8	8
	Limits	.....	12.5 - 14.3	12.5 - 14.3

TABLE 3.—*What a Man Should Weigh*

	Years									
Height, Cm.	19 Kg.	20 Kg.	21 and 22 Kg.	23 and 24 Kg.	25 to 29 Kg.	30 to 34 Kg.	35 to 39 Kg.	40 to 44 Kg.	45 to 49 Kg.	50 and Over Kg.
152.5	45	45	46	46	47	47	46	46	45	45
155	46	46	47	47	48	48	47	47	46	46
157.5	47	47	48	48	49	49	48	48	47	46
160	48	48	49	49	50	50	49	49	47	47
162.5	49	50	51	51	52	52	51	50	49	49
165	51	51	52	52	53	53	52	52	51	49
167.5	52	52	54	54	55	55	54	53	52	52
170	54	54	55	55	56	56	55	55	54	53
172.5	56	56	57	57	58	58	57	56	56	55
175	58	58	59	59	60	60	59	59	58	57
177.5	59	60	61	61	62	62	61	60	59	58
180	62	62	63	63	64	64	63	62	61	61
182.5	64	64	65	65	66	66	65	65	64	63
185	66	67	67	68	68	68	67	66	66	65
187.5	68	69	70	70	71	71	70	69	68	67
190	71	71	72	73	73	73	72	71	70	70

Lastly, the curves of the averages and limits of the transverse diameters of the hearts in all the groups, in all the ideal weight groups and in all the above-ideal weight groups were compared with the curves of other investigators: Cohn's [2] and Smith's [12] weight curves (table 5); Smith's [12] and Deutsch, Kauf and Warfield's [1] height curves (table 6); Deutsch, Kauf and Warfield's [1] age curves (table 7).

TABLE 4.—*Groups the Patients Would Be Classified In if of Ideal Weight for Height, Sq. Meters*

Groups, Sq. Meters		1.4 to 1.49	1.5 to 1.59	1.6 to 1.69	1.7 to 1.79	1.8 to 1.89
1.4 to 1.49	Average, cm.	13.6	....	....	....	....
	Numbers	1	....	....	....	....
	Limits, cm.	....	....	....	....	....
1.5 to 1.59	Average, cm.	12.9	12.7	....	....	....
	Numbers	6	1	....	....	....
	Limits, cm.	12.3-13.9	....	....	....	....
1.6 to 1.69	Average, cm.	12.4	12.5	12	....	....
	Numbers	4	27	9	....	....
	Limits, cm.	11.8-12.9	10.1-14.2	10.5-13.2	....	....
1.7 to 1.79	Average, cm.	14.5	12.5	12.9	12.6	....
	Numbers	1	13	65	2	....
	Limits, cm.	....	11.6-13.5	10.5-15	12.5-12.8	....
1.8 to 1.89	Average, cm.	....	13.8	13.2	13.2	13.5
	Numbers	....	6	47	61	2
	Limits, cm.	....	13-14.6	11.3-16	11-15.7	13.4-13.7
1.9 to 1.99	Average, cm.	....	....	13.7	13.7	13.4
	Numbers	....	....	5	18	22
	Limits, cm.	....	....	13.4-14.2	13.3-14.5	12.3-13.9
2 to 2.09	Average, cm.	....	....	....	13.7	13.6
	Numbers	....	....	....	2	6
	Limits, cm.	....	....	....	13.6-13.8	12.5-14.3

TABLE 5.—*Cohn's and Smith's Weight Curves* *

Cohn's Cases		Smith's Cases	
Weight, Kg.	Transverse Diameter, Cm.	Weight, Kg.	Transverse Diameter, Cm.
53	13.0	55	11.9
54	11.9	56	11.6
55	12.8	57	12.3
56	12.8	58	12.5
57	11.9	59	12.7
58	11.8	60	12.7
59	12.0	61	12.0
60	12.3	62	12.3
61	11.9	63	11.8
62	12.5	64	12.6
63	12.6	65	12.9
64	12.7	66	13.1
65	12.6	67	13.1
66	12.4	68	13.3
67	13.7	69	13.1
68	13.2	70	13.5
69	13.3	71	13.3
70	13.1	72	13.6
71	13.4	73	13.7
72	13.2	74	13.8
73	14.5	75	13.7
74	13.4	76	13.6
75	13.2	77	13.7
76	14.5	78	13.8
77	12.5	79	13.7
78	14.2	80	13.7
83	13.5	81	13.7
86	13.8	82	13.5
		83	13.7
		84	13.7

* From Cohn, A. E., An Investigation of the Size of the Heart in Soldiers by the Teleroentgen Method, Arch. Int. Med. **25**: 504 (May) 1920. Smith, B.: Teleroentgen Measurements of the Heart of Normal Soldiers, Arch. Int. Med. **25**: 525 (May) 1920.

COMMENT

Comparison of the average transverse diameters of hearts in the various body surface area groups shows that for persons of ideal weight (table 2) they are smaller than for those of the above-ideal weight or for the entire group, while the averages of the above-ideal weight and of the entire group are practically the same.

TABLE 6.—*Smith's and Deutsche, Kauf and Warfield's Height Curves* *

Smith's Cases		Deutsch, Kauf and Warfield Cases	
Height, Cm.	Transverse Diameter, Cm.	Height, Cm.	Transverse Diameter, Cm.
155	12.0	131-140	20.7
157	13.1	141-150	21.9
160	12.7	151-160	23.3
163	12.2	161-170	24.2
165	12.7	171-180	24.5
168	12.9	181-190	25.5
170	12.9	191-200	25.1
173	13.3		
175	12.6		
178	13.0		
180	13.3		
183	13.5		
185	13.5		

* From Smith, B.: Teleroentgen Measurements of the Hearts of Normal Soldiers, Arch. Int. Med. **25**: 525 (May) 1920 and Deutsch, Kauf and Warfield, Heart and Athletics, p. 36.

TABLE 7.—*Kauf and Warfield's Age Curves* *

Deutsch, Kauf and Warfield Cases					
Age	Transverse Diameter, Cm.	Age	Transverse Diameter, Cm.	Age	Transverse Diameter, Cm.
10	9.9	19	11.4	28	12.1
11	10.1	20	11.5	29	11.8
12	10.2	21	11.5	30	11.9
13	10.0	22	11.6	31	11.8
14	10.6	23	11.6	32	12.2
15	11.2	24	11.8	33	11.7
16	11.2	25	11.8	34	12.2
17	11.1	26	11.7	35	12.2
18	11.4	27	12.0	36-40	11.8

* From Deutsch, Kauf and Warfield, Heart and Athletics, p. 37.

The range between the largest and smallest transverse diameters of the hearts in the ideal weight group is less than in either of the other groups, while it is practically the same in the above-ideal weight group and in the entire group. It would therefore appear that the high averages for the transverse diameter of the heart and the wide range in size in each group were due to those cases in which the weight was above the ideal for the height.

If one compares the curves of ideal weight cases according to body surface area with curves based on height (table 6), weight (table 5) and age (table 7), it will be noted that the rise is more consistent.

When one compares the average transverse diameters of the hearts in the above-ideal weight group subdivided according to the body surface area group this group would have been in if the weight had been ideal with the averages in the ideal weight group, it is evident that the averages of the former are greater than of the ideal weight group of the same body surface area (table 8), and that the greater the above-ideal weight the greater is the deviation from the average for the ideal weight (tables 4 and 8).

TABLE 8.—*Comparison of Heart Diameters of the Above-Ideal Weight, Classified According to Their Ideal Weight, with Those of the Ideal-Weight Group**

Skin Surface Area Groups, Sq. Meters	Ideal Weight Group: Transverse Diameter, Average, Cm.	Above-Ideal Weight Cases (Subdivided According to the Surface Area Group They Would be in if of Ideal Weight for Height) Averages, Cm.
1.4 to 1.49	....	12.9; 12.4; 14.5
1.5 to 1.59	11.9	12.5; 12.5; 13.8
1.6 to 1.69	12.3	12.9; 13.2; 13.7
1.7 to 1.79	12.2	13.2; 13.7; 13.7
1.8 to 1.89	12.9	13.4; 13.6
1.9 to 1.99	13.2	
2 to 2.09		

* Only one case in the ideal weight group for skin surface area 1.4 to 1.49 square meters; therefore this average is not used.

TABLE 9.—*The Transverse Heart Diameter Averages of the Above-Ideal Weight Group, Classified as of Ideal Weight and Compared with the for Height, Sq. Meters**

Skin Surface Area Groups, Sq. Meters	Ideal Weight Group: Transverse Diameter, Average, Cm.	Above-Ideal Weight Cases (But in the Same Skin Surface Area Group as if of Ideal Weight for Their Height) Averages, Cm.
1.4 to 1.49		
1.5 to 1.59	11.9	12.7
1.6 to 1.69	12.3	12
1.7 to 1.79	12.2	12.6
1.8 to 1.89	12.9	13.5
1.9 to 1.99	13.2	
2 to 2.09		

* Only one case in the ideal weight group for skin surface area 1.4 to 1.49 square meters; therefore this average is not used.

Even the averages of the transverse diameters of the heart in the above-ideal weight subdivisions, which are still in the same body surface area group they would be in if the weight were ideal, are above the averages for the ideal group (table 9).

The largest transverse diameter of the heart for all groups in the ideal weight class is 14.2 cm., the lowest 10.6 cm., while the largest for the above-ideal weight group is 16 cm. and the lowest 10.1 cm.

Curves representing the transverse diameters of hearts in persons of ideal weight, the area of the body surface being used as a criterion,

include the following variables: height, weight, age, sex and diameter of the chest, indirectly concerned through its relation to weight.

CONCLUSIONS

1. Cases of ideal weight for height should be used in the estimation of the measurements of a normal heart.

2. The individual case of above ideal weight for height gives the greatest variation from the average transverse heart diameter or from the diameters of hearts of ideal weight.

3. The curves of average transverse diameters, body surface area being used as a criterion, show the least variation.

4. As the area of the body surface as computed also includes other variables, it approaches a clinical criterion for the estimation of the size of the normal heart.

Book Reviews

MODERN MEDICAL MONOGRAPHS. Edited by HUGH MACLEAN, M.D., D.Sc., F.R.C.P., Professor of Medicine, University of London.

THE ENDOCRINES IN GENERAL MEDICINE. By A. LANGDON BROWN, M.S., M.D., F.R.C.P., Physician to St. Bartholomew's Hospital. Price, $3. Pp. 134 with index, no reference to the literature and no illustrations. New York: Paul B. Hoeber, 1927.

This latest endocrine monograph in English is, according to the preface, "chiefly a record of the author's personal experience, first in the laboratory and later with patients." Besides the usual chapters on the individual glands and group of diseases, the author assays prophesy in the last chapter headed by the title "The Future of Endocrines." The thymus and pineal gland are discussed under the heading "The Retarding Glands." The monograph is easily read, the style being pleasing and clear, but the chief merit of the book is its brevity. The author says that his main aim is service to the general practitioner. It is to be regretted that so much unproved theory, speculation, disproved assertions and out and out nonsense should be served out as an aid to the practitioner in medicine who really needs guidance in this difficult field.

The following quotations justify the above stricture: As evidence of the physiologic effects of feeding the anterior lobe of the pituitary, the author cites the following: "Mr. Crossley-Meates has kindly informed me that he gave 2 grains of anterior lobe extract daily to an Irish wolfhound bitch-pup four months old. In a month the facial expression became heavy and the ears large, so that it resembled a bloodhound. The long bones were definitely larger and heavier than those of the rest of the litter. But the most striking difference of all was the change in character, for this bitch-pup would domineer over the rest of the litter, including the dog pups, and at eight months old she was more masculine and rougher in play than they were." This is medicine of 1927 almost at its worst. The following seems more appropriate from a writer of fiction than a guide of medical men: "The pituitary seems to play a special part with regard to rhythmic functions, and on the psychical side to show this in the direction of music and dancing, or on the more intellectual side with mathematical or more imaginative interests, widely as the last two seem to differ."

And what about the following? "A young man of 23 was brought to see me, who had been very late in learning to walk and talk. He showed me two photographs of himself taken at the age of 4 or 5—one of these looked like a normal child while the other looked degenerate. By the age of 6½ he had developed the habit of lying. He grew rapidly to the height of 6 feet 5 inches. His palatal arch was very high and his knuckles were very large. He was a confirmed liar and thief and was suspected of deliberate and wilful arson—the fossa becoming too small for the gland, the patient is apt to develop moral and intellectual inferiority, to suffer from compulsions and obsessions and to lack inhibitions. As Berman puts it, such individuals are 'pathological liars with little or no initiative or conscience.'"

On page 111 the author quotes with apparent approval the speculation that the anterior lobe of the pituitary tends to produce virile characters and the posterior lobe feminine characters and adds this charming bit of evidence: "We are all familiar with the inseparable couple of women friends. One of the two usually adopts a somewhat masculine role, and I have been struck on several occasions to note the number of signs she presents of overactive anterior pituitary."

On page 113 the author states that "persistence of the thymus produces, in addition to status lymphaticus physically," a "mother's darling psychologically."

On the question of testicular transplantation the author quotes Dr. Kenneth Walker with approval to the following effect: "Up to the present time I (Dr. Walker) have performed Steinach's operation on fifteen cases, and although it is difficult to eliminate the element of suggestion I believe that in at least half of these cases an improvement in general health and an increase in mental vigor have taken place. I am particularly inclined to recommend the operation in the treatment of that hopeless malady of later life, paralysis agitans, having seen a very marked improvement in two out of four cases which I have treated in this way. . . . It is frequently advisable to combine testicular grafts with the use of extracts of other endocrine glands, notably of the pituitary, the suprarenals or the thyroid."

The author refers to pituitary extract again and again as a lactagogue, although it was shown many years ago that it has no influence on the production of milk except to retard it when pituitary extract is used in large doses, and despite the growing evidence that the hormone of the parathyroid gland is ineffective when given by mouth, the author persistently refers to the therapeutic effects by giving parathyroid material by mouth. In the same way the author seems to be unfamiliar with much of the work which tends to show that diabetes insipidus is due to injury of the brain and not to hypofunction of the posterior lobe of the hypophysis, and that obesity associated with Fröhlich's syndrome is of brain origin and not an index of depression of the function of the anterior lobe of the hypophysis.

After completing the book the reader will have the impression that the author is a charming fellow, disinclined to question or contradict, with little infomation, and much faith. In view of the general poor and unreliable character of the book, it is surprising to find that the best chapter is (no. 11) headed "Endocrine Therapy." To be sure we meet even here such statements as "oral administration of parathyroid extract certainly seems to be effective," and "extracts of the whole pituitary gland should be given in cases of defective growth and development." He puts forth a rather weak argument for pluriglandular therapy but adds at once, "One must admit that pluriglandular therapy is generally irrationally applied."

The author seems most confused in the field of the pituitary gland. On page 64 he says, "Under action of the posterior lobe may lead to general obesity or localized fatty deposits. Of the latter type Dercum's disease—adiposis dolorosa—is a good example. . . . The disease is refractory in treatment, but I have seen decided benefit from thyroid extract together with injections of pituitrin, especially when combined with a suitable diet for obesity." This is not only pluriglandular therapy, it is shotgun therapy. The adipose patient thus treated will probably lose some weight but losing weight on such management does not help us discover the cause of the adiposity. The monograph is not a serious contribution to the theory and practice of medicine. It will be a hindrance rather than a help to the progress of general practice.

THE SIGNIFICANCE OF THE PHYSICAL CONSTITUTION IN MENTAL DISEASE. By F. I. WERTHEIMER, Phipps Psychiatric Clinic, and FLORENCE E. HESKETH, Johns Hopkins Hospital. Medicine Monograph Series. Price, $2.50. Pp. 76 with illustrations. Baltimore: Williams & Wilkins Company.

The authors present a compact discussion of their theme, defining the human constitution for the purpose of their investigation as "the correlative unity of those morphological, physiological and psychobiological developments of the individual which are definitely more influenced by heredity than by environment." Classifications of body types beginning with Hippocrates' "habitus apoplecticus" and "habitus phthisicus" and leading on up to Kretchmer's athletic, pyknic and asthenic groupings are tabulated and critically discussed.

The material of this study consists of sixty-five male patients chosen at random from the Phipps Institute, Johns Hopkins Hospital and a Maryland state hospital. Psychiatric, observational and anthropomorphic data were not

compared until the final correlation. Classification of morphologic types was made according to Kretchmer's descriptive method.

The authors' research contribution consists of the formulation—after the calculation and analysis of about thirty-seven different mensural indexes in each patient—of an index relating leg length to chest diameters and trunk length:

$$\text{Index} = \frac{\text{Leg length } 10^3}{\text{Transverse chest diameter} \times \text{sagittal chest diameter} \times \text{trunk height}}$$

The numerical values thus obtained are charted in a convincing manner to show no overlapping of values thus obtained in clear observation types so far as the pyknic and athletic-asthenic groupings are concerned. The average values for the three types are distinct.

The psychiatric correlations are interesting and demonstrate the value of Kretchmer's work. The authors appear to have made a decided contribution to psychiatry, and mental hygiene, in giving a reliable check on mere observation which is so apt to lead one astray.

A four page bibliography is not the least valuable portion of a brief monograph representing an infinite amount of labor.

KLINISCHE GASSTOFFWECHSELTECHNIK. Von DR. H. W. KNIPPING, Privatdozent an der Medizinischen Klinik der Universität Hamburg, and DR. H. L. KOWITZ, Professor an der Medizinischen Klinik der Universität Hamburg. Paper. Price, 18 marks. Pp. 193, with 72 illustrations and 2 tables. Berlin: Julius Springer, 1928.

This is a compact, accurate and useful little monograph on methods of basal metabolic studies for clinical purposes. While the German physiologists, especially Voit and Rubner, were the leaders in establishing the laws of nutrition and metabolism, the practical application of these principles in the clinics was essentially perfected and applied in the United States, and there are several monographs in English dealing with this subject. The present volume, therefore, presents to English readers nothing essentially new on the subject, except in the way of a model of compact and accurate presentation. Various European apparatus are described that are not in general use in this country, but these apparatus do not appear to have a great advantage over those in common use in this country. The appendix contains the necessary tables and charts for rapid calculations.

QUESTIONS PHYSIOLOGIQUES D'ACTUALITE. LEON BINET, Professeur agrege de Physiologie a la Faculté de Médecine de Paris. Paper. Price, 18 francs. Pp. 227, with 57 illustrations. Paris: Masson & Cie, 1927.

This monograph contains twenty-four chapters or lectures given as conferences on problems in physiology in the medical faculty of the University of Paris during the year 1925-1926. It is in no sense a textbook or monograph covering the whole aspect of physiology, but the author has taken a number of problems, such as sleep, tobacco, the spleen, cerebral circulation and others and has developed the present status of these problems in the light of experimental and clinical data. It is well written and concise, but in many cases superficial, discussion of many problems that are important in both fundamental physiology and medicine. Some of the chapters or lectures refer to the fundamental or important literature on the subject.